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# SARS-CoV-2 Infection and Cardiovascular Disease: COVID-19 Heart



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Coronavirus disease (COVID-19) is a serious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The symptoms of the disease range from asymptomatic to mild respiratory symptoms and even potentially life-threatening cardiovascular and pulmonary complications. Cardiac complications include acute myocardial injury, arrhythmias, cardiogenic shock and even sudden death. Furthermore, drug interactions with COVID-19 therapies may place the patient at risk for arrhythmias, cardiomyopathy and sudden death. In this review, we summarise the cardiac manifestations of COVID-19 infection and propose a simplified algorithm for patient management during the COVID-19 pandemic.

## Keywords

COVID • Coronavirus • CV disease • Myocarditis

## Background

Coronavirus disease (COVID-19) originated in the Wuhan province of China in late 2019 and is a serious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is genetically related to the coronavirus responsible for the SARS outbreak in 2002 [1]. The infection has spread globally and was declared a pandemic by the World Health Organization (WHO) on 11 March, 2020. The number of confirmed cases and deaths continue to rise daily.

The clinical manifestations of COVID-19 may range from asymptomatic or mild respiratory symptoms to severe life threatening respiratory and cardiac failure (Tables 1 and 2, Figure 1) [2–6]. Among 72,314 patients with COVID-19 in China, the clinical severity was reported as mild in 81.4%, severe in 13.9% and critical in 4.7% of patients [2]. In a recent study from New York, the most common presenting symptoms were cough (79.4%), fever (77.1%), dyspnoea (56.5%), myalgias (23.8%), diarrhoea (23.7%), and nausea and vomiting (19.1%) [7]. The primary cause of death in COVID-19 infection is respiratory failure but cardiac manifestations

may contribute to overall mortality and even be the primary cause of death in these patients (Table 3) [3,7–11]. Concomitant cardiovascular (CV) conditions are present in 8–25% of overall COVID-19 infected population and in a higher proportion of those who die [7,10,12–16]. A meta-analysis of eight studies from China (46,248 patients) showed a higher prevalence of hypertension (17±7%) and diabetes mellitus (8±6%) followed by cardiovascular disease (5±4%) in COVID-19 patients [10]. In another analysis of 44,672 cases from the Chinese Center for Disease Control and Prevention, a higher case fatality rate was noted among patients with pre-existing comorbid conditions (10.5% for CV disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer) compared to the overall case-fatality rate of 2.3% in the entire cohort [2]. Medications used for the treatment of COVID-19 infection can also increase overall cardiovascular risk [12].

## Pathophysiology of SARS-CoV-2

SARS-CoV-2 contains four structural proteins, namely spike (S), envelope (E), membrane (M), and nucleocapsid

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**Table 1** Stages of COVID-19 infection.

Stages	Pathogenesis	Symptoms	Signs	Proposed Therapeutic Strategies Based on Limited Data
1	Viral response/early infection	Constitutional Respiratory Gastrointestinal	Mild leukopaenia, lymphopenia. Elevated PT, D dimer, LDH, CRP; ferritin; IL6. Procalcitonin may be normal	Antimicrobial therapy Reduce Immunosuppressants if needed
2	Inflammatory phase/pulmonary phase	Shortness of breath Hypoxia: PaO <sub>2</sub> /FiO <sub>2</sub> ratio < 300	Increasing Inflammatory markers including cardiac biomarkers (Troponin, BNP) Abnormal CT chest	Supportive care. Restrictive IV fluid strategy. Antimicrobials, Immunotherapy per ID.
3	Hyperinflammatory phase/Cytokine release storm	ARDS SIRS, Sepsis Cardiac failure Multiorgan dysfunction, Shock, DIC	Markedly elevated inflammatory markers, cardiac biomarkers	Antimicrobial, Immunotherapy per ID. Supportive care including vasoactive drips if indicated.

Abbreviations: PT, prothrombin time; LDH, lactate dehydrogenase; CRP, C reactive protein; IL6, interleukin 6; CT, computed tomography; ID, infectious disease; IV, intravenous; ARDS, acute respiratory distress syndrome; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation.

(N) proteins of which S protein mediates the viral entry into host cells [17,18]. The virus exhibits strong binding to cell-associated and soluble angiotensin converting enzyme (ACE) 2 receptors expressed in many organs such as the heart, kidneys, intestine, lung, brain and liver [19,20]. COVID-19 infected patients thus present with a spectrum of atypical gastrointestinal manifestations, cardiac and renal injury, neurological and acute respiratory symptoms [16,19,21]. In the lungs, the virus leads to endothelial and microvascular dysfunction, alveolar exudative inflammation, interstitial inflammation and fibrosis, and focal bleeding which causes severe respiratory manifestation of the disease [22–24]. Coronavirus particles have been observed in the ciliated columnar epithelial cells of bronchiolar mucosa [23].

After gaining entry into the cells via ACE2 receptors, SARS-CoV-2 down-regulates the ACE2 expression such that the enzyme is unable to exert organ protective effects [25]. ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) upregulate the number of ACE2 receptors on the surface of myocardial, alveolar and gastrointestinal cells which has raised the concern of ACEI and ARB induced increase in COVID-19 acquisition into the myocardial and alveolar cells [19,22,26,27]. However, renin angiotensin aldosterone system (RAAS) blockade has been shown to reduce the exposure to SARS-CoV-1 spike protein induced acute lung injury in experimental mouse models [19,28–31]. A lower rate of severe COVID-19 disease and a trend toward a lower level of interleukin-6 (IL-6), and increased CD3 and CD8 T cell counts in the peripheral blood and a decreased peak viral load has been observed in patients taking ACEI and ARB [32]. ACEI and ARB therapy may therefore be protective in low level viraemia and trials of losartan on COVID-19 patients are ongoing [9,25,33,34].

COVID-19 related immune response may be multiphasic as illustrated in a recent elegant article by Siddiqi et al. (Table 1) [4].

Similar to an influenza outbreak, myocardial injury due to COVID-19 may be related to increased viscosity, heightened coagulation cascade, pro-inflammatory effects or endothelial cell dysfunction caused by SARS-CoV-2 virus [35,36]. In a recent study of COVID-19 patients, there was cardiomyocyte hypertrophy, degeneration and necrosis of cardiomyocytes, mild interstitial hyperaemia and oedema along with infiltration of lymphocytes, monocytes and neutrophils but no virus component in the myocardial tissue [23,37]. In another autopsy report, there was scattered individual cell myocyte necrosis with lymphocytes adjacent to, but not surrounding, degenerating myocytes, which may represent an early manifestation of a viral myocarditis [24]. The pericytes may be infected by SARS-CoV-2 virus and cause capillary endothelial cell or microvascular dysfunction leading to individual cell necrosis [22–24]. Myocardial injury in patients with COVID-19 infection could be multifactorial which include atherosclerotic plaque rupture, coronary vasospasm, hypoxic injury to the vasculature, direct endothelial or formation of microthrombi [37]. Myocardial injury and fulminant myocarditis can occur from direct viraemic effect on the myocardial cells and secondary effects from the body's hyperimmune response to the virus and overall systemic inflammatory response [9].

Increasing levels of inflammatory markers such as C-reactive protein, D-dimer, ferritin, IL-6 and lactate dehydrogenase (LDH) has been associated with higher mortality in COVID-19 patients, possibly due to cytokine storm or secondary haemophagocytic lymphohistiocytosis [11,38–41]. SARS-CoV-2 can activate the coagulation cascade leading to thrombocytopenia and sometimes severe hypercoagulability and its sequelae such as ischaemia of the finger and toes

**Table 2** Clinical features and management tool.**COVID like mild symptoms**

Stay at home and monitor vitals if able

Self-quarantine

14 days if testing not feasible

Avoid ER if haemodynamically stable and no clinical worsening.

Supportive care till more

definitive treatment recommendation

**Day 1–5: Early viral prodrome STAGE 1: Observe or Admit if risk factors or COVID+ and more than mild symptoms**

Observe at home if haemodynamically stable or admit if increased risk assessment score like SOFA, patients with comorbidities (age >65, male, hypertension, chronic disease, diabetes, immunocompromised, malignancy) or haemodynamically unstable

**Day 5–10 Inflammatory pulmonary phase STAGE 2:**

**Admit if:** Cardiopulmonary: Increased shortness of breath, hypoxia or other unstable vitals, ECG changes, worsening labs.

**Day > 9: Hyperinflammatory/cytokine release STAGE 3:****ICU level care**

Sepsis

Hypoxia/ARDS

Cardiac failure

Multiorgan dysfunction

Shock

Disseminated intravascular coagulation

**Diagnostic tests:**

- CBC: Lymphopaenia, thrombocytopenia
- CMP: Elevated liver function tests
- Coagulation: PT/INR, D dimer
- LDH, CRP; fibrinogen, ferritin, procalcitonin
- Infection: viral panel, blood, urine, sputum cultures, symptom specific cultures and imaging.
- Cardiac biomarkers: Troponin, BNP
- Telemetry: Continuous QTc monitoring on high risk therapy or pathology
- ECG to assess ischaemia, myopericarditis, QTc, rhythm
- Echocardiogram if clinically indicated (symptoms, BNP troponin elevation, ECG changes, shock)
- Cortisol level (if persistent hypotension)
- CT chest without contrast for pneumonia evaluation, with contrast to rule out PE in suspected cases with significant D dimer elevation or atrial arrhythmias

**Follow-up tests: as needed**

- ECG: Repeat if QTc prolonging medications.
- ESR, CRP, LDH, ferritin, D dimer, IL-6, procalcitonin
- Troponin; NT ProBNP
- Mixed/central venous saturation (daily if shock)

**Supportive therapy:**

- Supplemental oxygen to maintain oxygen saturation 90–96%
- Early intubation/ARDS lung protective strategy
- Avoid aerosolisation. Do not disconnect from ventilator without following the precautionary steps even during code.
- Avoid unnecessary transportation; encourage bedside procedure when feasible with full PPE.

Abbreviations: CBC, complete blood count; CMP, complete metabolic profile; NTpBNP, N terminal pro brain natriuretic peptide; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; PE, pulmonary embolism; PPE, personal protective equipment; LDH, lactate dehydrogenase; ECG, electrocardiograph; CT, computed tomography; INO, inhaled nitric oxide.

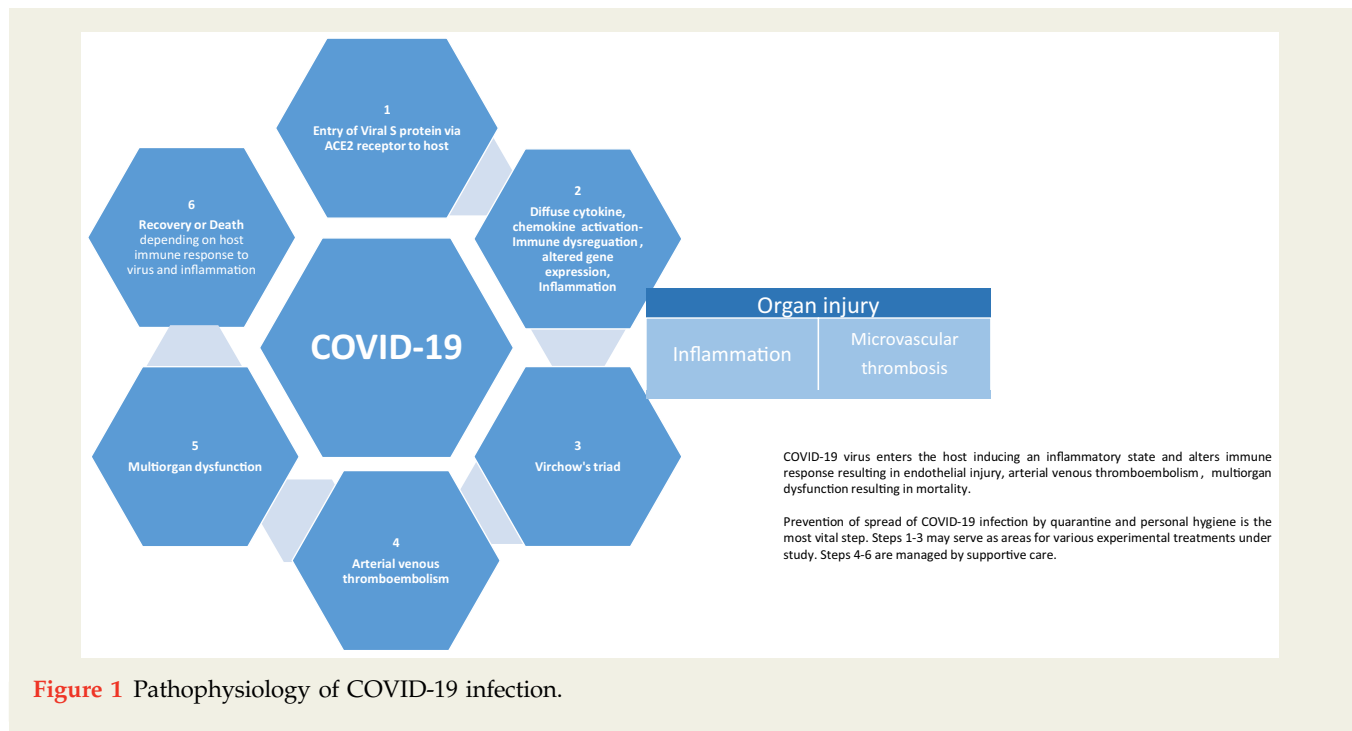
[10,42,43]. The higher incidence of venous and arterial thromboembolism despite prophylactic anticoagulation in these patients is likely due to excessive inflammation, hypoxia, immobilisation and diffuse intravascular coagulation, and some physicians have even used tissue plasminogen activator (tPA) with some improvement in acute respiratory distress syndrome (ARDS) [44,45].

## Cardiovascular Manifestations of SARS-CoV-2

### Myocardial Injury, Acute Coronary Syndrome and Myocarditis

Myocardial injury, defined as elevation in cardiac troponin concentration above the 99<sup>th</sup> percentile of upper reference limit, has been observed in 7–17% of hospitalised COVID-19 patients

[10,38,39,46–49]. Furthermore, the incidence of myocardial injury as reported from China increases with the severity of illness, rising to 22.2% of patients needing ICU care and 59% of patients that died [10,50]. Acute coronary syndrome (ACS) can be one of the initial presentations of COVID-19 infection which may range from ST elevation myocardial infarction (STEMI) to Takotsubo cardiomyopathy [10,41,51]. Myocardial ischaemia and infarction could be secondary to plaque rupture triggered by a virus-induced stress response or from thrombosis secondary to hypercoagulability [10,36]. Myocardial supply-demand mismatch can cause Type 2 MI [46]. In a recent series of 18 COVID patients from New York, who had STEMI during initial presentation (n=10) or during hospitalisation (n=8), there was variability in presentation, a high prevalence of nonobstructive disease (33% of those who underwent cardiac catheterisation), and a poor prognosis (72% mortality) [41]. Acute virus-negative lymphocytic myocarditis has been associated with SARS-CoV-2 respiratory infection, with some



reports showing improvement in cardiac biomarkers after treatment with lopinavir/ritonavir and hydroxychloroquine [52,53]. Any rise in serum troponin level should be interpreted in the context of the clinical scenario and results of further evaluation by invasive angiography or coronary computed tomography (CT) angiogram (Table 4) [54]. High risk patients may need admission to the hospital for further management as per clinical practice guidelines but low risk patients can be discharged from the emergency department after discussing the appropriate follow-up plan in case of recurrent symptoms [55].

### Cardiac Arrhythmia

Elevated cytokine levels can lead to a systemic inflammatory response and myocardial injury, both of which can predispose to atrial and ventricular arrhythmias. New onset malignant tachyarrhythmias, such as sustained monomorphic ventricular tachycardia (VT) and polymorphic VT in the setting of elevated cardiac biomarkers, should raise the suspicion for myocarditis. In 137 patients admitted for COVID-19 disease in Hubei province, heart palpitations were noted as one of the presenting symptoms in 7.3% of patients [15,56]. In another study of 138 hospitalised COVID-19 patients, arrhythmia was noted in 16.7% of patients and was more common in those patients admitted to the intensive care unit (ICU) compared to non-ICU patients (44.4% vs. 6.9%,  $p < 0.001$ ) [50]. There have been reports of complete heart block and atrial fibrillation in patients with COVID-19 infection [57,58].

### Heart Failure and Cardiogenic Shock

Increased inflammatory cytokines and respiratory distress can cause exacerbation of pre-existing left ventricular (LV) dysfunction or lead to a new onset cardiomyopathy. New

onset LV dysfunction may represent myocarditis, stress cardiomyopathy or myocardial ischaemia, all of which increase the risk of death [10]. In a study by Zhou et al., the incidence of heart failure was significantly higher in non survivors from the infection compared to survivors (52% vs 12%,  $p \leq 0.0001$ ) [10]. Right heart failure is likely to occur due to elevated pulmonary artery pressure from pulmonary complications [16]. In early stages, exacerbation of heart failure with preserved ejection fraction can occur due to aggressive fluid resuscitation attempts, and in the later stages of disease when cytokine levels rise, acute systolic heart failure leading to cardiogenic shock has been reported [10].

### Cardiac Effects of COVID-19 Treatment

The clinical manifestations of COVID-19 infection and medication side effects pose challenges to physicians taking care of these patients. Various antivirals, antimalarial and immunomodulating medications, glucocorticoids and convalescent plasma from recovered patients have been used for the treatment of COVID-19 with variable results (Table 5) [3,50,59–66]. The Infectious Disease Society of America recently published guidelines regarding COVID-19 treatment (Table 6) [67]. Chloroquine and hydroxychloroquine cause alkalinisation of the intracellular phagolysosome and thus cause under-glycosylation of ACE2 receptors required for cellular entry of COVID-19, which prevents virion fusion and uncoating [59,60]. Hydroxychloroquine with or without azithromycin has been shown to decrease viral carriage in recent small studies [59]. However, there was no evidence of clinical efficacy of hydroxychloroquine in patients

**Table 3 Summary of cardiovascular disease management in COVID-19 patients.**

Clinical Features	Suggested Management
Ischaemic heart disease, myocarditis, myocardial injury	
NSTEMI	<ul style="list-style-type: none"> <li>• Check ECG and troponin if clinical suspicion of acute coronary syndrome (ACS)</li> <li>• Guideline directed medical therapy: aspirin, heparin, statin, beta blocker (if no bradycardia or cardiogenic shock)</li> <li>• Assess drug interaction of antiplatelet or anticoagulants</li> <li>• Cardiac catheterisation if high clinical suspicion of acute coronary occlusion</li> <li>• Coronary CT angiogram in haemodynamically stable NSTEMI</li> </ul>
STEMI	<ul style="list-style-type: none"> <li>• Activate STEMI team per hospital protocol</li> <li>• Primary PCI for STEMI, thrombolytic therapy is controversial, use for low risk STEMI only if interventional cardiologist unavailable</li> <li>• Bedside echocardiogram if any clinical uncertainty</li> <li>• If no angiographic disease- monitor and treat myocarditis sequelae-heart failure; arrhythmia; thromboembolism and risk factor modification.</li> </ul>
Myocardial injury Myocarditis Stress induced Cardiomyopathy	<ul style="list-style-type: none"> <li>• Echocardiogram to assess LV function</li> <li>• Troponin trend to differentiate from Type I MI and assess prognosis along with BNP</li> <li>• Monitor for arrhythmia, consider EP consult if malignant arrhythmia</li> <li>• Inotropes and vasopressor support if haemodynamic instability with LV dysfunction.</li> <li>• Discuss antiviral and anti-inflammatory therapies approved to use.</li> <li>• Guideline directed medical therapy for cardiomyopathy</li> <li>• Exercise limitation for 3–6 months to prevent sudden cardiac death.</li> </ul>
Cardiac arrest	<ul style="list-style-type: none"> <li>• Address goals of care early and periodically in all patients</li> <li>• Follow standard ACLS protocol</li> <li>• Consider mechanical CPR device if available</li> <li>• Use proper PPE per hospital protocol prior to initiating resuscitative efforts</li> <li>• Minimise code team size to prevent exposure to health care providers</li> </ul>
Heart failure and cardiogenic shock	
Heart Failure	<ul style="list-style-type: none"> <li>• BNP, troponin and echocardiogram to assess new onset HF</li> <li>• Telemetry for arrhythmia detection and monitoring</li> <li>• Standard HF management with daily weight, intake/output, diuresis, monitoring electrolytes and renal function</li> <li>• Limited fluid and blood product administration due to high risk of cardiopulmonary decompensation. Concentrate drips when able.</li> <li>• Avoid nonsteroidal anti-inflammatory agents</li> <li>• Continue ACEI/ARB/ARNI in otherwise stable patients who are at risk for, being evaluated for, or with Covid-19 unless hypotensive or renal failure.</li> <li>• Coronary CT angiogram for ischemic workup for new LV dysfunction if no ongoing ischaemia.</li> </ul>
Shock	<ul style="list-style-type: none"> <li>• Cardiac catheterisation if HF suspected due to acute coronary syndrome.</li> <li>• SBP&lt;90 for &gt;15 mins with impaired organ perfusion, Urine output &lt;30 m/hr.</li> <li>• Recognise delayed presentation of mechanical complications of myocardial infarction or peritonitis from bowel ischaemia related to low perfusion state.</li> <li>• Check mixed venous saturation to differentiate different types of shock.</li> <li>• Conservative fluid resuscitation, crystalloid preferred over colloid.</li> <li>• Norepinephrine to stabilise shock; transition to inotrope when clinically indicated.</li> <li>• Inhaled pulmonary vasodilators (INO preferred) should only be administered through a closed system to prevent risk from aerosolisation.</li> <li>• Evaluate alternate aetiologies of shock if haemodynamics not improving.</li> <li>• Discuss with interventional cardiology regarding activating shock team.</li> <li>• ECMO and mechanical circulatory support device in highly selected cases.</li> </ul>

Table 3 (continued).

Clinical Features	Suggested Management
Transplant patient Immunosuppression	<ul style="list-style-type: none"> <li>• Discuss with heart transplant or cardiology team regarding reducing immunosuppression especially anti metabolites due to risk of infections.</li> <li>• Stress dose steroids for adrenal insufficiency for those on chronic steroids</li> </ul>
Arrhythmia Prolonged QTc	<ul style="list-style-type: none"> <li>• Telemetry monitoring and at least daily QT assessment</li> <li>• EP evaluation if QTc &gt;450 msec in the absence of bundle branch block or &gt;500 with bundle branch block if being started on antiarrhythmic or other QT prolonging medication.</li> <li>• Monitor electrolytes; Keep K &gt;4.5, Mg &gt;2.2</li> <li>• Monitor for QT prolongation if on QT prolonging medications</li> <li>• <math>QTc = QT / \sqrt{RR}</math> interval (in sec, Bazett correction). QTc will approximately be equal to QT if HR 60–70 bpm.</li> </ul>
Polymorphic VT Sustained VT Ventricular fibrillation Torsades de Pointes (TdP)	<p><i>Key thresholds:</i></p> <ul style="list-style-type: none"> <li>• If QTc <math>\geq 470</math> ms in males and <math>\geq 480</math> ms females but &lt;500 ms: close surveillance and stop QT prolonging medications</li> <li>• If QTc &gt;500ms or &gt;550 ms with BBB or increase in QTc &gt;60 ms after drug initiation: place pacer pads, stop QT prolonging medication and maintain HR &gt;80 bpm with isoproterenol or dobutamine.</li> <li>• Advanced cardiac life support protocol if haemodynamic compromise</li> <li>• Follow guideline recommended antiarrhythmic therapy for specific conditions. Discussion with cardiology/electrophysiology team.</li> <li>• Amiodarone bolus 150 mg IV in non-code setting; Isoproterenol + Lidocaine or temporary pacing if bradycardia induced torsade de pointes.</li> <li>• Monitor electrolytes: Keep K &gt;4.5, Mg &gt;2.2</li> <li>• <b>VT:</b> Amiodarone 150 mg bolus then infusion 1 mg/min if QTc &lt;450 ms (300 mg IV if code); Avoid amiodarone if QTc markedly prolonged.</li> <li>• <b>VT:</b> Lidocaine if QTc &gt;550 ms: bolus 75–100 mg then infusion 0.5–2 mg/min, avoid if poor hepatic function or severe heart failure</li> <li>• Discuss antiarrhythmic drug choice if QTc borderline (450–550 msec) with cardiology/EP.</li> <li>• <b>TdP/polymorphic VT:</b> Maintain heart rate of &gt;80 bpm (may need beta agonist such as dobutamine, isoproterenol or epinephrine; transvenous pacing).</li> <li>• Magnesium IV 2–4 gm for Torsade de Pointes</li> <li>• Limited bedside Echo for LV dysfunction evaluation.</li> <li>• Non-sustained polymorphic VT requires immediate patient assessment as cardiac arrest may follow.</li> </ul>

**Table 3 (continued).**

Clinical Features	Suggested Management
SVT including AF/AFL with heart rate > 150 bpm	<ul style="list-style-type: none"> <li>• ACLS protocol if haemodynamically unstable.</li> <li>• Lenient rate control, allow permissive tachycardia.</li> <li>• SVT: Adenosine 6–12 mg IV push in acute management</li> <li>• SVT, AF/AFL: beta blocker may be preferred over calcium channel blocker depending on LV function</li> <li>• AF: if rhythm control desired, may use amiodarone.</li> <li>• Cardiology or EP consult before considering class Ic antiarrhythmics (flecainide, propafenone)</li> <li>• Discuss with cardiology if QTc&gt;450 ms on a QT prolonging drug or QTc&gt;500 ms or QTc increase after started on a QT prolonging drug.</li> <li>• Assess interaction of oral anticoagulant with antivirals.</li> </ul>
Bradycardia	<ul style="list-style-type: none"> <li>• Follow standard bradycardia guidelines (AHA, ACLS) if patient unstable.</li> <li>• Discontinue AV nodal blocking agents.</li> <li>• Assess medication interaction with antivirals (Table 5).</li> </ul>

Abbreviations: PCI, percutaneous coronary intervention; LV, left ventricle; HF, heart failure; SVT, supraventricular tachycardia; AF, atrial fibrillation; AFL, atrial flutter; EP, electrophysiology; ACLS, advanced cardiac life support; AKI, acute kidney injury; SBP, systolic blood pressure; BBB, bundle branch block; ms, milliseconds; ECMO, extracorporeal membrane oxygenation; VT, ventricular tachycardia; AHA, American Heart Association; AV, atrioventricular.

hospitalised for COVID-19 infection with oxygen requirement in a recent French study of 181 patients [68]. Chloroquine and hydroxychloroquine, which have been used in small studies of COVID-19 patients with variable clinical outcomes, carry a risk of prolonging the QTc interval and torsade de pointes due to blockade of the KCNH2-encoded hERG/Kv11.1 potassium channel [59,60,69,70]. Electrolyte abnormalities and concomitant use of QT prolonging agents may further increase the risk of fatal arrhythmias in these high risk patients [69]. Chloroquine can also inhibit CYP2D6 which will, in turn, raise the levels of beta blockers (metoprolol and carvedilol) and thus necessitate close monitoring of blood pressure and heart rate [71].

Antiviral medications used in the treatment of COVID-19 also have side effects. Lopinavir/ritonavir may cause bradycardia, QT and PR interval prolongation [62,69,72] and ribavirin can affect warfarin dosing [73]. Similarly, lopinavir/ritonavir can increase levels of rivaroxaban, apixaban and ticagrelor, and decrease levels of clopidogrel and prasugrel due to the interaction with cytochrome P450 enzymes [74–77]. Tocilizumab and sarilumab, IL-6 receptor blockers, have shown some promising results for the treatment of cytokine release syndrome or secondary haemophagocytic lymphohistiocytosis [78]. In a recent cohort of patients hospitalised for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement in respiratory status was observed in 68% of patients [58]. A National Institutes of Health (NIH) clinical trial also showed 31% faster recovery from advanced COVID-19 infection when treated with remdesivir [79]. When a 5-day course of remdesivir was compared with a 10-day course in phase 3 clinical trial (GS-US-540-5773), there was similar improvement in clinical status and

the side effects were nausea, elevated liver enzymes and respiratory failure [80]. However, in another study of adult patients with severe COVID-19 infections admitted to Chinese hospitals, remdesivir was not associated with a statistically significant difference in time to clinical improvement [81]. Based on these findings, the Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) for emergency use of remdesivir for the treatment of hospitalised COVID-19 patients. Many of the side effects of newer investigational medications are still to be evaluated [82,83].

## Approach to Cardiac Management in Patients With COVID-19 Infection

The highly infectious nature of the COVID-19 infection and transmission risk to health care workers makes it challenging to manage patients with suspected or confirmed infection. Tables 2 and 3 and Figure 2 summarise a proposed diagnostic approach to a patient suspected of COVID-19 infection and management of their cardiovascular conditions. Sequential Organ Failure Assessment (SOFA) and a quick SOFA score may be helpful to assess the severity of the illness and some hospitals have used this as an initial triage tool [10,84,85]. There should be emphasis on minimising exposure of the health care professionals to the viral infection by performing limited bedside testing such as echocardiogram and telemetry to assess QT interval rather than a formal complete echocardiogram and electrocardiograph (ECG) [86].



**Table 4** Procedures during COVID-19 infection.

Noninvasive Procedures	
Transthoracic echocardiogram	<ul style="list-style-type: none"> <li>• Suspected HF, ACS or new arrhythmia due to cardiomyopathy</li> <li>• Consider focussed protocol pertaining to diagnosis of interest.</li> <li>• Do bedside echocardiogram first when feasible and limit frequent echo</li> </ul>
Transoesophageal echocardiogram	<ul style="list-style-type: none"> <li>• High-risk for aerosolisation, and use should be restricted unless absolutely essential for a diagnosis that will change short-term management.</li> <li>• Assess for endocarditis only if Duke Criteria met and transthoracic not diagnostic.</li> <li>• Pre cardioversion, only if patient unstable or unsafe to wait for 4 weeks on anticoagulation</li> <li>• Severe valvular regurgitation or stenosis if urgent intervention planned or if diagnosis unclear by transthoracic echocardiogram.</li> <li>• Mechanical complication from myocardial infarction when not fully assessed by TTE or catheterisation</li> </ul>
Cardiac MRI and CT	<ul style="list-style-type: none"> <li>• Cardiac CT angiogram in stable NSTEMI or diagnostic uncertainty in ACS cases.</li> <li>• Cardiac MRI if myocarditis diagnosis would change treatment approach.</li> </ul>
Invasive Procedures	
Interventional/Structural	<ul style="list-style-type: none"> <li>• Unnecessary, non-urgent procedures pose high risk to health care providers.</li> <li>• Consider bedside procedures when feasible to minimise risk.</li> <li>• Coronary angiogram for STEMI and high-risk NSTEMI</li> <li>• Right heart catheterisation: Avoid unless necessary, e.g., HF diagnosis uncertain and clinical suspicion of mixed or refractory shock where information will change management.</li> <li>• No routine endomyocardial biopsy in stable patients.</li> </ul>
Electrophysiology	<ul style="list-style-type: none"> <li>• Urgent procedures only, e.g, pacemakers, ICD for secondary prevention, ablation for haemodynamically significant arrhythmia not controlled with medications or cardioversion, cardioversion for symptomatic arrhythmia, lead revision for a pacemaker dependent patient, generator change for battery at end of life for a pacemaker dependent patient.</li> <li>• Defer non-urgent procedures, SVT, VT ablation, AF ablation in the stable patient.</li> </ul>

Abbreviations: MRI, magnetic resonance imaging; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; SVT, supraventricular tachycardia; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; HF, heart failure; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; CT, computed tomography; ACS, acute coronary syndrome; TTE, transthoracic echocardiogram.

## Respiratory Management

Supplemental oxygen to maintain oxygen saturation above 90%, early intubation and use of low tidal volume and high positive end expiratory pressure (PEEP) are recommended in the management of respiratory distress (Table 2, Figure 2) [87,88]. Patients with COVID-19 infection require close monitoring of respiratory status with a low threshold for

intubation to minimise the risk of aerosolised respiratory secretions, and prevent high-risk emergency intubations [87]. Early stages of respiratory infection can be challenging to differentiate from cardiogenic pulmonary oedema in patients with a prior diagnosis of heart failure and a serum brain natriuretic peptide (BNP) level and myocardial imaging may be helpful. Routine right heart catheterisation should be

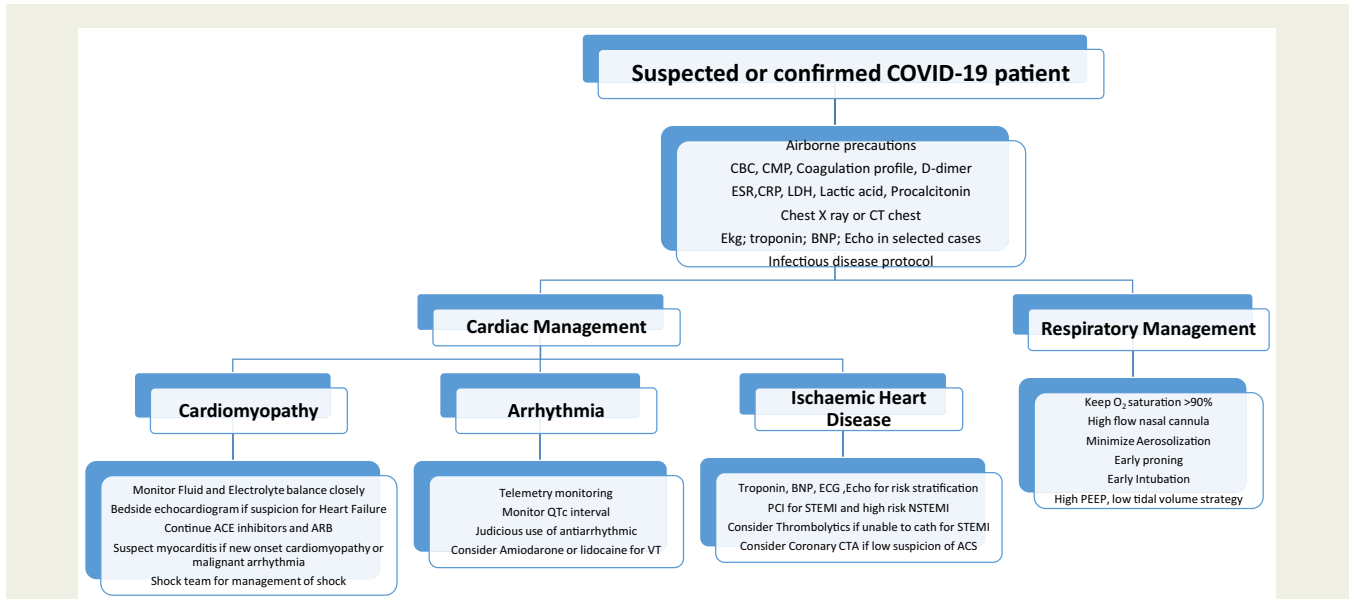
**Table 5** Medications used in COVID-19 infection and drug interaction.

COVID Therapy	Interaction	Cardiovascular Related Effects
Chloroquine hydroxychloroquine	Inhibition of lysosomal enzymes in the myocyte CYP2D6 inhibition	QT prolongation ↑beta-blocker effect (metoprolol and carvedilol)
Azithromycin	QT prolonging drugs Electrolyte imbalance	QTc prolongation
Lopinavir/ritonavir	Avoid other QT prolonging drugs Avoid electrolyte imbalance CYP3A4 inhibition	QTc, PR interval prolongation ↑Ticagrelor level ↓Clopidogrel, Prasugrel level
Ribavirin and lopinavir/ritonavir	Warfarin, Apixaban, Rivaroxaban	Increased bleeding risk with factor Xa inhibitors

**Table 6 COVID-19 treatment recommendations.**

Anti-COVID 19 Therapies	Drugs	Mechanism	IDSA Recommendation April 2020	Comments
Antimalarial	<b>Hydroxychloroquine/ chloroquine</b> 400 mg bid × 1 d followed by 200 mg bid × total 5 d	Multiple mechanisms- reduces infection & immunomodulation by inhibiting viral entry, release.	Very low evidence. In the context of a clinical trial in hospitalised patients.	Monitor QTC and avoid if QTC > 500 msec or 550 msec if paced or BBB. Bone marrow suppression, retinopathy and cardiomyopathy. Contraindicated if epilepsy or porphyria
	Hydroxychloroquine/ chloroquine plus <b>Azithromycin</b> 500 mg 1 d; 250 mg × 4 d	Azithromycin, antibacterial has shown anti-inflammatory effects in other infectious disease.	Very low evidence. In the context of a clinical trial in hospitalised patients.	If concomitant bacterial pneumonia suspected. Monitor QTC and avoid if QTC > 500 msec or 550 msec if paced or BBB. Qtc prolonging combination drugs should be avoided.
Antiviral	<b>Lopinavir/ritonavir</b> and other HIV-1 protease inhibitors 400/100 mg bid oral × 10 d	Inhibits HIV-1 protease that lead to the formation of immature, noninfectious viral particles.	Very low evidence. In the context of a clinical trial in hospitalised patients	Combination increases serum lopinavir. Multiple drug interaction due to CYP3A inhibition Serious gastrointestinal side effect and skin eruptions.
	<b>Remdesivir</b> 200 mg IV loading dose, followed by 100 mg IV daily 5–10 d	Premature termination of viral RNA transcription	No formal recommendations at this time.	Compassionate use protocol in pregnant women. Monitor liver enzymes and consider renal dose adjustment
Corticosteroids	<b>Prednisone</b>		No clinical evidence of net benefit. Against the routine use of corticosteroids in hospitalised patients.	Risk of delayed viral clearance, risk of secondary infection, more adverse effects and increase mortality has been postulated.
	<b>IV methyl prednisone</b> <b>IV Hydrocortisone</b>		Use of corticosteroids in the context of a clinical trial in hospitalised patients with ARDS	Or if treating another condition like asthma, COPD or secondary adrenal insufficiency (chronic prednisone > 10 mg daily) or refractory shock
Interleukins-6 (IL-6) blocker tocilizumab	<b>Tocilizumab,</b> Siltuximab, Sarilumab	IL-6 inhibition and prevents T cell activation	Very low evidence. Only in the context of a clinical trial in hospitalised patients.	Risk of opportunistic infections must be tested. Severe allergic reactions, hepatic failure and intestinal perforations have been reported with the drug.
Passive artificial immunity	<b>COVID-19 convalescent plasma</b>	Obtained from recovered healthy donors may suppress viraemia	Very low evidence. In the context of a clinical trial in hospitalised patients.	
	<b>Intravenous immunoglobulin</b>	Protective antibodies from community recovered from COVID-19	Unknown at this time	
Active artificial immunity	<b>Vaccine</b> <b>NCT04283461</b>	Are antigenic and induce protective immunity in host.		Clinical trial phase.

Abbreviations: BBB, bundle branch block; COPD, chronic obstructive pulmonary disease.



**Figure 2** COVID-19 treatment algorithm.

Abbreviations: CBC, complete blood count; CMP, complete metabolic profile; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; LDH, lactate dehydrogenase; CT, computed tomography; EKG (also ECG), electrocardiograph; BNP, NTpBNP, N terminal pro brain natriuretic peptide; Echo, echocardiograph; VT, ventricular tachycardia; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; CTA; computed tomography angiography; ACS, acute coronary syndrome.

avoided due to the potential exposure risk to health care workers (Table 3).

## Haemodynamic Management

Patients with COVID-19 infection are prone to fluid overload from aggressive resuscitation attempts, acute kidney injury in critically ill patients and treatment with steroids in those with chronic lung disease, and therefore require close monitoring of fluid balance and electrolytes. This is critical in very ill patients, many of whom may have new onset or worsening heart failure [87,89] and are prone to rapid fluctuations in blood pressure and heart rate. Norepinephrine is recommended as the first line vasoactive drug in shock and vasopressin can be added if hypotension persists, although currently there is no data about their use in these patients (Table 2) [87].

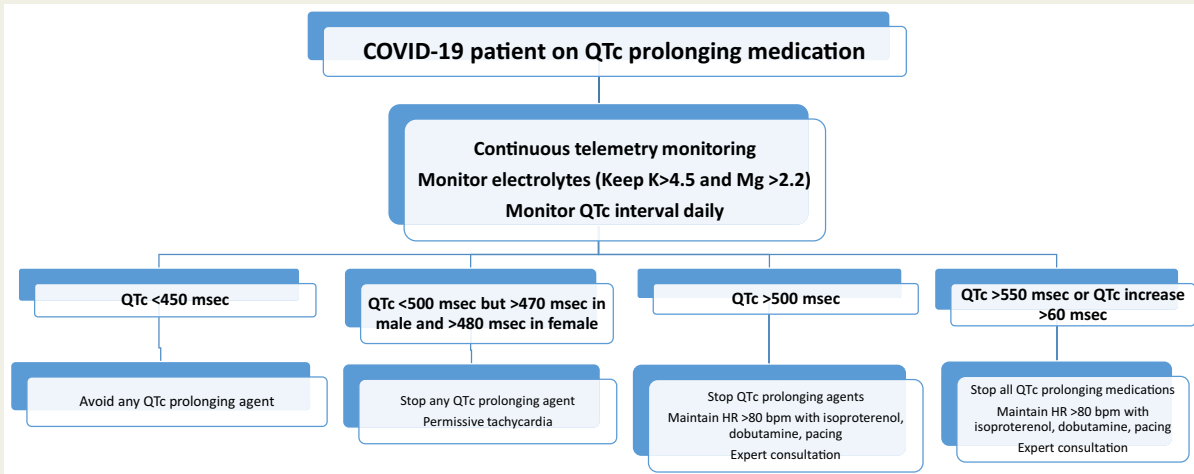
## Cardiovascular Monitoring

### Arrhythmia

Hospitalised patients with COVID-19 infection should have telemetry monitoring, since these patients can have various cardiovascular manifestations and are at risk of arrhythmia. The antimicrobial and immunomodulating medications used for treatment of COVID-19 can have a proarrhythmic risk, including QT interval prolongation (Table 3). Hydroxychloroquine and azithromycin have a high risk of QT prolongation and drug interactions [83,90], and the risk associated with this combination must be reassessed. Avoiding unnecessary QT prolonging agents, monitoring

electrolytes and use of isoproterenol or dopamine infusion to increase heart rate in patients with bradycardia can prevent arrhythmic complications (Table 5, Figure 3) [69,90]. Tisdale and colleagues have developed a scoring system for predicting QTc prolongation in hospitalised patients which may be a useful tool to assess the risk of QTc prolongation [91]. Recent guidance or recommendation from Mayo Clinic authors is that if there is QTc prolongation >500 msec or increase in QTc >60 msec after initiation of COVID-19 treatment, consideration has to be given to stop medications or reverse QTc prolonging effect [69,92]. In another recent case report, late sodium channel blocking agents like lidocaine bolus infusion improved QTc interval in a patient with COVID-19 infection to enable treatment with hydroxychloroquine and azithromycin [90].

Management of atrial and ventricular arrhythmias is otherwise similar to those without COVID-19 infection but using caution with drug interactions and QTc prolongation [93–95]. There have been some anecdotal reports of sudden death, sinus node dysfunction and atrioventricular nodal disease in COVID-19 patients. The aetiology of such sudden death is still unclear but given the possibility of ventricular arrhythmias, prolonged ambulatory monitoring may be needed. Electrophysiology procedures such as ablation of atrial and ventricular arrhythmia should be postponed until recovery from acute illness to prevent virus transmission (Table 4) unless the procedure is deemed to be lifesaving or has haemodynamic consequences as recommended by groups including the CSANZ Heart Rhythm Council COVID-19 Pandemic working group [96,97].



**Figure 3** Prolonged QTc management algorithm.

### Ischaemic heart disease

Primary percutaneous coronary intervention (PCI) is the recommended treatment strategy for ST-elevation myocardial infarction (STEMI) (Table 3, Figure 2) [54,98]. Alternative therapeutic options such as systemic fibrinolytic therapy was used in China and there has been discussion among the interventional cardiology community, Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship (SCAI ELM) Members and Graduates, regarding consideration for fibrinolytic therapy in low risk STEMI patients (e.g. inferior STEMI without right ventricular involvement or lateral myocardial infarction without haemodynamic compromise) [98]. It is important for regional centres to have equitable access to thrombolytics and stock rotation systems are imperative to ensure supply [99]. Patient transfer to a higher level of care should be limited but should be performed in a timely manner when required [99]. Patients with high risk non ST-elevation MI (NSTEMI) also need urgent invasive evaluation but in low risk NSTEMI patients or in those where serum troponin level elevation is not clearly suggestive of Type 1 MI, obtaining a coronary CT angiogram can stratify the extent of coronary artery disease (CAD) and help with the decision regarding invasive coronary angiography [54]. Echocardiography and advanced imaging (e.g. magnetic resonance [MRI]) can differentiate myocarditis with diffuse myocardial dysfunction from acute coronary syndromes where a focal wall motion abnormality in the distribution of a specific coronary artery is observed (Table 3). Stable patients with symptoms suggestive of COVID-19 should be tested for infection prior to the procedure due to the risk of aerosol transmission to procedural staff. In patients with diagnosed COVID-19 infection, invasive procedures (e.g. intra-aortic balloon pump, pericardiocentesis, extracorporeal membrane oxygenation, temporary transvenous pacemaker, etc.) can be performed at the bedside rather than in the cardiac catheterisation

laboratory to minimise the infection risk to health care workers (Table 4) [98,100]. The elevation in serum troponin or BNP levels could be nonspecific in patients with COVID-19 infection, and clinicians should use their medical judgement in suspected cases of acute MI or heart failure and follow the latest recommendations from the guiding societies [16,54]. It is also important to be mindful of delayed presentations of common cardiovascular pathology during COVID-19 pandemic as there has been a significantly reduced number of STEMI cases in the hospital and increase in out of hospital cardiac arrest [101,102].

### Cardiogenic shock

Shock in COVID-19 infection could be primarily cardiogenic from acute heart failure or myocarditis but may be multifactorial, as cardiac involvement often complicates respiratory failure and sepsis [10,48]. Serum BNP, echocardiography and troponin level can help clarify the degree of cardiac involvement (Figure 2) [103]. Routine endomyocardial biopsy and cardiac MRI to evaluate malignant arrhythmia or myocarditis should not be performed [103]. The utility of extracorporeal membrane oxygenation (ECMO) in the management of shock in COVID-19 patients is unclear [104]. Most patients with cardiogenic shock complicating COVID-19 illness die despite aggressive treatment, as one case series from China reported 83% mortality despite ECMO use [105]. It is therefore important to identify the contribution of cardiac, pulmonary and systemic causes of shock when considering mechanical respiratory and circulatory support with ECMO [106]. Evaluation by a multidisciplinary shock team consisting of an interventional cardiologist, heart failure specialist and cardiac surgeon is recommended to evaluate risks and benefits of ECMO in the individual patient [104]. Lack of sufficient health care resources during this pandemic raises ethical concerns around ECMO use and these calculations may change if effective therapies emerge [106].

## Impact of COVID-19 Infection on the Health Care System

COVID-19 infection has caused a negative impact on both the physical and mental health of health workers, and many health care workers and frontline workers including firefighters have been infected with the virus [107]. Implementation of stringent infection prevention protocols may have caused delayed care in many patients and have put health care workers into difficult clinical decision making situations [107]. However, a high level of compliance (>90%) with these protocols may be required to effectively control the spread of COVID-19 infection [108].

In a recent editorial, Allahwalla and colleagues have elegantly pointed out the long-term consequences of the COVID-19 related delay in care of chronic cardiovascular conditions and a possible second tsunami of acute cardiac conditions [102]. Therefore, there is a need for strategies to minimise, and prepare for, an impending second wave of acute medical conditions which may overwhelm the health care system and physicians [102]. Patients with cardiovascular conditions should continue to receive the health care services including preventive health services and efforts should be made to take advantage of telehealth services [99,109]. The psychological impact of the pandemic should be taken into consideration while evaluating patients [109].

## Conclusion

Cardiovascular manifestations of COVID-19 infection range from mild elevation of serum troponin and BNP levels to fulminant myocarditis, life-threatening arrhythmias and refractory shock. All patients need close haemodynamic and electrocardiographic monitoring especially if they are on COVID-19 treatment. While there are multiple ongoing clinical trials, there is currently insufficient data to support any definitive treatment option with antimicrobials or immunomodulators. Infection prevention and control measures such as social distancing and personal hygiene remain the cornerstone of management of this global pandemic.

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## Conflicts of Interest

None.

## Author Contributions

Bishnu P. Dhakal, MD (Conceptualisation, methodology, writing original draft, reviewing and editing), Nancy K. Sweitzer, MD, PhD (Reviewing and editing), Julia H. Indik, MD, PhD, FACC (Conceptualisation, reviewing, writing,

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