Cardiovascular Manifestations of COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the cause of COVID-19, was first reported in Wuhan, China. SARS-CoV-2 especially involves alveolar epithelial cells, which results in respiratory symptoms more severe in patients with cardiovascular disease (CVD) probably linked with increased secretion of angiotensin-converting enzyme 2 in these patients compared with healthy individuals. Cardiac manifestations may contribute to overall mortality and even be the primary cause of death in many of these patients. A higher prevalence of hypertension (HTN) followed by diabetes mellitus and CVD was observed in COVID-19 patients. A higher case-fatality rate was seen among patients with pre-existing comorbid conditions, such as diabetes, chronic respiratory disease, HTN, and cancer, compared to a lesser rate in the entire population. Cardiovascular (CV) manifestations of COVID-19 encompass a wide spectrum, including myocardial injury, infarction, myocarditis-simulating ST-segment elevation myocardial infarction, nonischemic cardiomyopathy, coronary vasospasm, pericarditis, or stress (takotsubo) cardiomyopathy. This review is intended to summarize our current understanding of the CV manifestations of COVID-19 and also to study the relationship between SARS-CoV-2 and CVDs and discuss possible mechanisms of action behind SARS-CoV-2 infection-induced damage to the CV system.

Key words: Acute coronary syndromes, arrhythmia, cardiovascular disease, COVID-19, myocardial injury, myocarditis, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the cause of COVID-19, was first reported to the World Health Organization (WHO) as a pneumonia in Wuhan, China, on December 31, 2019.[1] On January 31, 2020, the WHO characterized COVID-19 as a public health emergency, and on March 11, 2020, it was finally declared as a pandemic.[2] As of August 7, 2020, there are 19,360,443 confirmed worldwide cases of COVID-19 with over 719,619 deaths.[3]

SARS-CoV-2 especially involves alveolar epithelial cells, which results in respiratory symptoms. These tend to be more severe in patients with CVD and is probably linked to increased secretion levels of angiotensin-converting enzyme 2 (ACE2) in these patients as compared to healthy individuals.[4] The level of ACE2 in the heart and atherosclerotic vessels is increased in patients with coronary artery disease (CAD) and heart failure (HF).[5]

Invariably, the primary cause of death in COVID-19 infection is respiratory failure. However, cardiac manifestations may contribute to overall mortality and may even be the primary cause of death in many of these patients.[6-10] In 8%–25% of overall COVID-19-infected population, concomitant cardiovascular (CV) conditions are observed and this percentage is even higher among those who die.[7,9,11-15]

In a recent meta-analysis of eight studies (46,248 patients), a higher prevalence of hypertension (HTN, 17% ± 7%) followed by diabetes mellitus (8% ± 6%) and...
cardiovascular disease (CVD, 5% ± 4%) was observed in COVID-19 patients. In another study of 44,672 cases, a higher case-fatality rate (CFR) was seen among patients with pre-existing comorbid conditions (10.5% for CVD, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for HTN, and 5.6% for cancer) compared to the overall CFR of 2.3% in the entire population. In a retrospective study in which 191 patients were included of whom 137 were discharged and 54 died in hospital, 48% of patients had single comorbidity, with HTN being the most common 30%, followed by diabetes 19%, and coronary heart disease in 8% of patients.

CV manifestations of COVID-19 encompass a wide spectrum, including myocardial injury, infarction, myocarditis-simulating ST-segment elevation myocardial infarction (STEMI), nonischemic cardiomyopathy, coronary vasospasm, pericarditis, or stress (takotsubo) cardiomyopathy. Elevated cardiac biomarkers indicate an unfavorable prognosis. Guo et al. conducted a study on 187 patients with COVID-19 of whom 52 (27.8%) exhibited myocardial injury as demonstrated by elevated troponin T (TnT) levels. Mortality was markedly higher in patients with elevated TnT levels than in patients with normal TnT levels (59.6% vs. 8.9%). The highest mortality (69.44%) and shortest survival were seen in those with both elevated TnT levels and underlying CVD.

In a study by Shi et al. comprising 416 hospitalized patients from Wuhan, 82 (19.7%) patients with myocardial injury were compared to 334 (80.3%) patients without myocardial injury. In a study by Wang et al., it was observed that 16.7% of patients developed arrhythmia and 7.2% experienced acute cardiac injury as well as other COVID-19-associated complications. Some cases of acute-onset HF, myocardial infarction (MI), myocarditis, and cardiac arrest have also been reported.

Huang et al. reported that 12% of patients with COVID-19 were diagnosed as having acute myocardial injury, which is shown by elevated levels of high-sensitive troponin I (hsTnI).

Based on early reports, patients with CVD may represent 25% of those in an intensive care unit (ICU) plus those with HTN accounting for 58% of patients. In addition, Zhou et al. found that myocardial injury, defined by raised serum cardiac troponin I (cTnI) levels, in COVID-19 patients was associated with over 50% mortality rate. Furthermore, HF was prevalent in 23% of patients presenting with COVID-19, which was also more prevalent among patients who died compared to those who survived (51.9% vs. 11.7%). These reports provide evidence of cardiac involvement as a possible late phenomenon of the viral respiratory infection.

This review is intended to summarize our current understanding of the CV manifestations of COVID-19 and also to study the relationship between SARS-CoV-2 and CVDs. We will discuss also possible mechanisms of action behind SARS-CoV-2 infection-induced damage to cardiovascular system.

### CARDIOVASCULAR MANIFESTATIONS

To outline the spectrum of CV presentations of COVID-19 is a difficult task. Based on the current evidence, it appears that the CV sequelae may range from direct or indirect myocardial injury, myocarditis, possible acute coronary syndrome (ACS), cardiac arrhythmias, HF, and cardiogenic shock.

It is well known that the CV mortality is higher in influenza pandemics than in all other causes. Acute respiratory viral infections, such as coronaviruses, are known to trigger factors for CVD. During the current COVID-19 pandemic, an increased morbidity and mortality has been reported in the elderly population and in those with comorbid conditions.

The most prevalent comorbidities were HTN, diabetes, and CVDs. It is often difficult to differentiate between complications arising from comorbid conditions and possible direct CV damage by COVID-19 infection.

Patients presenting with pre-existing CVD appear to have heightened vulnerability to develop COVID-19 and tend to have more severe diseases with worse clinical outcomes. Various CV risk factors also adversely affect prognosis of these patients, although they do not seem to increase likelihood of developing the infection. A meta-analysis of six published studies from China including 1527 patients with COVID-19 reported 9.7%, 16.4%, and 17.1% prevalence of diabetes, cardio-cerebrovascular disease, and HTN, respectively.

Although the prevalence of diabetes and HTN in this cohort was same as in the Chinese general population, the prevalence of cardio-cerebrovascular disease was significantly higher. More importantly, the presence of diabetes, cardio-cerebrovascular disease, and HTN was associated with a 2-fold, 3-fold, and 2-fold greater risk of severe disease or requiring ICU admission, suggesting prognostic impact of these comorbidities. A much larger report from the Chinese Centers for Disease Control and Prevention described clinical outcomes in 44,672 confirmed cases of COVID-19. The overall CFR was 2.3% in the entire cohort but significantly higher (6%, 7.3%, and 10.5%, respectively) in patients with HTN, diabetes, and CVD.

In this review, COVID-19’s impact on the CV system will be divided into primary/direct or secondary/indirect cardiac involvement; there is, of course, considerable overlap between the two. Primary cardiac manifestations of COVID-19 disease include ACS, myocarditis, and arrhythmias. Secondary cardiac involvement is usually part of (due to) a systemic inflammatory syndrome and can manifest as acute myocardial injury/biomarker...
elevation and/or HF Congestive Heart Failure (CHF). Secondary cardiac involvement is often accompanied by the evidence of other end-organ damage. Finally, we will review additional vascular complications of COVID-19 disease.

**PATHOPHYSIOLOGY OF CARDIAC MANIFESTATION OF COVID-19**

SARS-CoV-2 is caused by an enveloped, positive-sense, single-stranded RNA beta-coronovirus. Seven species of these beta-coronaviruses are known to cause human infections, with four mainly causing mild flu-like symptoms and the remaining three resulting in potentially fatal illnesses (SARS, Middle East respiratory syndrome [MERS], and the current COVID-19). Although the respiratory tract is the primary target for SARS-CoV-2, CV system may be involved in several different ways.\[11,29\]

SARS-CoV-2 enters human cells by binding to ACE2, a membrane-bound aminopeptidase which serves many physiological functions in the lungs, heart, kidneys, and other organs.\[30\] ACE2 plays an important role in the neurohumoral regulation of CV system in normal health as well as in various disease conditions. It is highly expressed lung alveolar cells, which provides an explanation for the respiratory symptoms experienced by patients with COVID-19.\[31\]

More than 7.5% of myocardial cells have positive ACE2 expression, based on single-cell RNA sequencing,\[6\] which could mediate SARS-CoV-2 entry into cardiomyocytes and cause direct cardiotoxicity.\[8\] The binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signaling pathways, leading to acute myocardial and lung injury.\[11,29\]

More severe forms of COVID-19 are characterized by acute systemic inflammatory response and cytokine storm, which can result in injury to multiple organs, leading to multiorgan failure. Studies have shown high circulatory levels of pro-inflammatory cytokines in patients with severe/critical COVID-19.\[10,17\] Further, an abnormal T-cell and monocyte response have been observed in COVID-19 patients, leading to a systemic hyper-inflammatory response characterized by increased pro-inflammatory cytokine and chemokine production (tumor necrosis factor [TNF], interleukin [IL]-2, IL-6, IL-7, and CCL2 among others).\[7\]

Macrophage activation syndrome-like manifestations, classically associated with rheumatic diseases including Kawasaki disease,\[32\] have also been reported in COVID-19 patients supporting the hypothesis that the increase of Kawasaki-like presentations could be a result of COVID-19-induced systemic hyper-inflammation and consequent vasculitis.\[33\] Xiong et al. observed that plasma TnT levels were significantly positively linear correlated with plasma high-sensitivity C-reactive protein (CRP) levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis.\[34\]

Huang et al.\[10\] also highlighted that in patients with COVID-19, the cytokine storm resulted from an imbalance between T helper 1 and T helper 2 responses, itself leading to myocardial injury. The release of inflammatory cytokines after infection may cause reduction in coronary blood flow, decrease in oxygen supply, destabilization of coronary plaque, and micro-thrombogenesis.\[35\]

Increased cardiometabolic demand associated with the systemic infection coupled with hypoxia caused by acute respiratory illness can impair myocardial oxygen demand–supply relationship and lead to acute myocardial injury.\[36\] Myocardial injury can be the result of a mismatch between myocardial oxygen supply and demand, being classified as type 2 MI.

Severe respiratory complications and subsequent hypoxia are common findings in patients with COVID-19. In a meta-analysis of 19 studies, including a total of 2874 patients, the most predominant chest X-ray finding was bilateral pneumonia, with ground-glass opacity being reported in 68.5% of patients.\[38\] In addition, ground-glass opacity was the most frequent chest CT finding (97.6%) in a Chinese cohort of 83 patients with COVID-19–related pneumonia and was associated with severe outcomes in all (100%) patients.\[39\]

Systemic infection and fever increase the metabolic needs of peripheral tissues and end organs, resulting in a rise of metabolic demands of the myocardial cells.\[40\] The associated tachycardia decreases diastolic perfusion time which may lead to inadequate subendocardial perfusion in patients with CAD, resulting in cardiac injury.\[41\]

Systemic inflammation as well as increased shear stress can precipitate plaque rupture, resulting in acute MI. Prothrombotic milieu created by systemic inflammation further increases the risk.\[38\] Vascular endothelium is an active organ with paracrine, autocrine, and endocrine functions, which is vital for the regulation of vascular tone and the maintenance of vascular homeostasis. Endothelial dysfunction is the primary factor of microvascular dysfunction characterized by vasoconstriction and subsequent organ ischemia, inflammation associated with tissue edema, and a procoagulant state.\[42\]

Varga et al.\[43\] observed the direct viral infection of endothelial cells in several patients, all of whom had underlying conditions including HTN, kidney disease, CAD, and diabetes mellitus.\[43\] The presence of viral particles within endothelial cells and an accumulation of inflammatory cells, with the evidence of endothelial and inflammatory cell death, have been described...
by authors, suggesting that SARS-CoV-2 infection facilitates endotheliitis as a direct consequence of viral involvement and of the host inflammatory response. Moreover, it has been suggested that the induction of apoptosis and proptosis might have an important role in endothelial cell damage in patients with COVID-19. COVID-19–endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. Various antiviral drugs, corticosteroids, and other therapies aimed at treating COVID-19 can also have deleterious effects on the CV system. Electrolyte imbalances can occur in any critical systemic illness and precipitate arrhythmias, particularly in patients with underlying cardiac disorder. There is particular concern about hypokalemia in COVID-19, due to interaction of SARS-CoV-2 with renin-angiotensin-aldosterone system (RAAS). Hypokalemia increases vulnerability to various tachyarrhythmias.

**ACUTE CORONARY SYNDROMES**

ACSs comprise a spectrum of disease entities ranging from non-STEMI (NSTEMI) and unstable angina to STEMI. The first two often termed collectively as NSTE-ACS differ in their pathophysiological characteristics from STEMI, in that they result from an acute nonocclusive thrombus overlaying a disrupted plaque. On the other hand, STEMI is usually attributable to an acute thrombosis overlaying a disrupted plaque, which is completely occlusive of the epicardial coronary artery. Some pathophysiological mechanisms can be implicated to explain the matter. As ACE2 receptors are also present in the vascular endothelial cells, direct viral infection can lead to plaque instability and type 1 MI. Severe systemic inflammatory response in the third phase of the disease may lead to plaque instability and rupture.

Microangiopathy has also been described to produce further coronary artery involvement. Such small-vessel involvement can be due to systemic vasculitis or due to microembolization from ACS or disseminated hypercoagulability impairing blood flow. Acute inflammation can lead to endothelial dysfunction, consequently causing vasoconstriction and ischemia in the sensitive organs such as heart. Furthermore, inflammation-induced endothelial dysfunction increases the risk of thrombosis and thrombotic events. In addition, fever and the surge of inflammation could increase the cardiac demand by increasing metabolism and heat rate, resulting in cardiac ischemia and cardiac events, particularly in patients with underlying CVD.

Clayton *et al.* in a study have reported an association between recent respiratory infection and MI. This significant association was further highlighted in a meta-analysis of case–control studies. STEMI causes acute myocardial injury pattern on electrocardiography (ECG) and needs to be immediately treated to prevent irreversible myocardial damage. Timely reperfusion strategy is the treatment of choice. Of the two available reperfusion therapies, primary percutaneous coronary intervention (PCI) is preferable to fibrinolytic therapy because it is safer and more effective. On the other hand, moderate- and high-risk NSTE-ACS patients who are medically stabilized can be treated with an urgent, but not necessarily emergent, invasive strategy (i.e., coronary angiography with intent to revascularize).

STEs seen in COVID-19 patients often have nonobstructive coronary disease which further adds to the complexity of treating these patients. Banglore *et al.* reported a case series comprising of 18 patients who developed ST-segment elevation with Covid-19 in New York. Among these 9 patients underwent coronary angiography. Of these nine patients, three had no obstructive CAD and 5/6 with obstructive disease underwent PCI (one after receiving thrombolytics). Hence, nonobstructive disease was observed in one-third of the patients who underwent coronary angiography. These cases of STE with no obstructive coronary disease on angiography may be related to perimyocarditis, although the pathophysiology remains under investigation. The prognosis of STEMI presentation in the setting of COVID-19 was worse with a 72% rate of in-hospital mortality.

Interestingly, mortality in patients with nonobstructive coronary lesion was higher (90%) than among those with obstructive lesions (50%), although the absolute numbers were limited. Stefanini *et al.* studied 28 patients in Italy with STEMI and COVID-19. It was observed that STEMI represented the first clinical manifestation of COVID-19 in the majority of cases (85.7%). Early mortality was 39.3%. Of note, angiography demonstrated the absence of obstructive CAD in 39.3% of cases. The high prevalence of STEMI mimics in this population further emphasizes the need for angiography (either invasive or noninvasive) as opposed to empiric fibrinolytic therapy, given the potential for harm when administering fibrinolytics for non-ACS presentations.

A study done in Hong Kong evaluated primary PCI in seven patients presenting with STEMI and calculated the time from onset of symptoms to medical contact to be a median of 318 min, compared with a median of 82.5–91.5 min recorded in the previous year. During the peak time of COVID-19 outbreak patients with STEMI presented significantly late after the onset of
symptoms as compared to normal times the previous year. Similarly, the door-to-device time was almost 30 min longer, at a median of 110 min, compared with a median of 84.9 min the previous year. When put in the context of existing data on door-to-balloon (D2B) time and CV outcomes, while 60–90 min estimates the absolute risk reduction of 1-year mortality at 2.4%, the odds worsens when this time increases to 90–120 min. In the same study, an incremental increase in the D2B time by 1 h was associated with a 64% increase in 1-year mortality. While COVID-19 may potentially increase the risk of ACS, cath lab activations for STEMI in the United States (US) have decreased significantly during the pandemic. Among nine high-volume centers in the US, there was a 38% reduction in STEMI activations compared to the 14-month period before the pandemic. A similar finding was reported in Spain where there was a 40% reduction in STEMI activations. Although the reason for this is not clear, it is postulated that it may be related to patients’ fear of exposure to SARS-CoV-2 when presenting to the hospital.

It is unknown how many people worldwide may not be seeking medical care for possible ACS due to fear of COVID-19. It is possible that due to delays in seeking appropriate medical care, patients may eventually present to the hospital with HF, cardiogenic shock, or mechanical complications from ACS. Studies must be performed to assess the impact COVID-19 that could have on the CV mortality through such indirect mechanisms.

In the COVID-19 pandemic, the management of STEMI has been particularly difficult. Soon after presentation at the emergency department, multiple factors have been the cause of delay for a primary PCI approach, e.g., determining whether STEMI or COVID is the primary problem, and deciphering mimickers of STEMI, such as takotsubo cardiomyopathy, myocarditis, right ventricular (RV) failure, or massive pulmonary embolism (PE).

Screening for COVID infection may take time, and within the catheterization laboratory, additional time is needed for donning and doffing personal protective equipment. In addition, redeployment of staff has resulted in shortages to team availability. From a procedure room standpoint, cardiac catheterization laboratories are positive pressure rooms with a significantly higher risk of aerosolization, and therefore, some have been converted to negative pressure rooms, while others must be fitted with high-efficiency particulate air filters. In addition, specific protocols for anesthesia, emergent intubation, and protection of staff and equipment have been implemented, all of which add time to the care of these patients.

American College of Cardiology Interventional Council and Society for Cardiovascular Angiography and Intervention have issued statements regarding the management of STEMI during the COVID-19 pandemic, according to which primary PCI should remain the standard of care in these patients, with fibrinolytic therapy reserved for patients with relative contraindications, or those with severe bilateral COVID pneumonia or acute respiratory distress syndrome (ARDS), given their poor overall prognosis.

NSTEMI patients with suspected or confirmed COVID-19 should be managed by aggressive medical management. High-risk patients or hemodynamically unstable patients should be managed by early invasive strategy (<24 h), as in all patients with NSTEMI. A noninvasive or medical approach would be the best for low-risk patients.

During this pandemic, cardiologists have to face multiple challenges: on the one hand, there is the necessity to contain the spread of the infection; on the other hand, there is the increasing difficulty in identifying and treating patients with suspected or confirmed COVID-19 and contemporary cardiological urgencies; protocols are being constantly refined and updated, but clinical judgment will be fundamental too. For example, it is suggested that patients with STEMI and suspected COVID-19 infection should be treated by primary PCI only if they are at high cardiological risk, while low-risk cases can be treated with thrombolyis. Although this may be useful in the immediate period to contain the pandemic, the consequences of these new approaches are uncertain, and we will have evidence of this in the coming future.

**MYOCARDITIS**

Myocardial injury from SARS-CoV-2 infection may also occur via nonischemic mechanisms, such as acute and fulminant myocarditis and stress-induced cardiomyopathy.

SARS-CoV-2 has been associated with cases of myocarditis and acute decompensated HF. Myocarditis was initially reported in China by cases of cardiogenic shock and reduced left ventricular ejection fraction (LVEF) among COVID-19 patients. These patients had extremely elevated levels of cardiac biomarkers (namely troponin, creatine kinase [CK]-MB, and brain natriuretic peptide [BNP]) and required inotropic or extracorporeal membrane oxygenation (ECMO) support to maintain adequate cardiac output.

Based on the clinical presentation and elevations in biomarkers, these cases were diagnosed as “fulminant myocarditis” and were treated with a combination of steroids, intravenous immunoglobulins (IVIGs), antivirals, antibiotics, anti-inflammatory agents, renal replacement therapy, and mechanical ventilation.

There is new emerging evidence that SARS-CoV-2 has a similar effect on the myocardium as SARS-CoV and
MERS. Myocardial involvement has been confirmed in SARS-CoV-2-positive patients via magnetic resonance imaging (MRI) and endomyocardial biopsy.[65-67] Cardiac biopsy findings in COVID-19 patients have shown inflammatory infiltration of the myocardium with T-lymphocyte and macrophages, interstitial edema, and in some cases, evidence of cytoplasmic vacuoles, indicating direct viral involvement of the myocardial cells.[66,67]

In a postmortem case series of 68 patients in a cohort of 150 COVID-19 patients from China, 7% of patients died of circulatory failure with some degree of myocardial involvement, as marked by the elevations in troponin.[22] However, in 33% of cases, myocarditis could have played a contributing role to patient death.[23] However, it is unclear if these cases can truly be classified as myocarditis, given the lack of ejection fraction assessment via transthoracic echocardiogram (TTE), MRI, or biopsy. From a different case series in Seattle, WA, troponin elevation was seen in 15% of patients, but none of the patients who underwent TTE had evidence of a reduced ejection fraction.[6]

The differentiation between myocarditis and stress-induced cardiomyopathy can be challenging, since cardiac magnetic resonance (CMR) and/or biopsy are not available in most cases. Fried et al.[67] and Sala et al.[66] each reported a case of COVID-19 with mid-left ventricular (LV) or basal-to-mid-LV hypokinesia, a pattern of mid-ventricular, or reverse Takotsubo stress cardiomyopathy respectively.[27,66]

Sala et al.[66] reported on a 43-year-old woman with COVID-19 who presented with reverse takotsubo syndrome and mild LV systolic dysfunction. Cardiac magnetic resonance (CMR) revealed diffuse myocardial edema on the basal and mid-LV segments, with no detectable scar. Endomyocardial biopsy documented diffuse T-lymphocytic inflammatory infiltrates and huge interstitial edema without any other substantial damage. Molecular analysis showed the absence of the SARS-CoV-2 genome within the myocardium.[66]

The incidence of acute HF was 33% in critically ill patients with COVID-19 without a history of LV systolic dysfunction in Washington state.[68] Importantly, cardiomyopathy can develop in COVID-19 with mild or absent respiratory symptoms.[65] Although the clinical picture is still referred to as myocarditis in many instances, myocardial infection by SARS-CoV-2 was not proven in most cases with COVID-19 myocardial involvement.

To date, only isolated case reports provided data on the pathology of the myocardial tissue from COVID-19 patients, which preclude drawing definitive conclusions on this topic.[66,67] In a case report of a 69-year-old woman presenting with COVID-19 and cardiogenic shock, Tavazzi et al.[67] described, for the first time, a biopsy-proven myocardial localization of viral particles. Although the clinical presentation suggested severe and necrotizing acute myocarditis, the pathology report demonstrated only low-grade myocardial inflammation and absence of myocyte necrosis.[67]

Importantly, SARS-CoV-2 was only demonstrated in the interstitial cytopathic macrophages and their surroundings, whereas no viral particle was found in cardiac myocytes, which showed nonspecific damage (mainly focal myofibrillar lysis).[67] Either transient viremia or infected macrophage migration from the lung might occur in COVID-19 patients with nonacute myocardial involvement.

The available data seem to rule out a classic myocarditis presentation (i.e., direct infection of myocardial cells by the virus). Rather, it has been suggested that myocardial involvement in COVID-19 may be caused by the cytokine-release syndrome.[67]

A case reported by Hu et al.[63] from China described the evaluation of a 37-year-old man who presented with chest pain, dyspnea, and diarrhea and was found to have fulminant myocarditis with acute elevations in cardiac troponin T (cTnT) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) and LVEF of 27%, with normal coronaries on computed tomography coronary angiography. He was treated with IVIG and methyl prednisolone for immunosuppression, along with supportive care with vasopressors and diuretics, and ultimately had recovery of LV function (LVEF 66%) and improved biomarkers.[63]

A case report from Italy described a 53-year-old woman with confirmed SARS-CoV-2 infection who presented with fatigue, elevated cardiac biomarkers, ECG changes, and a depressed LVEF to 40% with diffuse hypokinesia. A cardiac magnetic resonance imaging showed increased wall thickness, diffuse biventricular hypokinesia, and diffuse late gadolinium enhancement involving most of the myocardium. Notably, her CRP was never elevated above the reference range, and she never suffered from respiratory failure. She was treated with antivirals, including lopinavir/ritonavir, and intravenous methyl prednisolone, and on day 6, a repeat echocardiogram showed partial recovery of her LVEF. This report suggests diffuse myocardial inflammation in some cases, rather than secondary inflammatory myocardial suppression.[69]

Other coronaviruses, including MERS-CoV, have been reported to cause acute myocarditis and HF.[14] It remains possible that, in some cases, SARS-CoV-2 causes myocardial dysfunction through viral myocarditis; however, at the point of this writing, pathological evaluation of suspected cases of COVID-19–associated myocarditis, including the possibility of viral entry into cardiomyocytes, is extremely limited. The coronary microvasculature and endothelium may be at risk for viral entry due to ACE2 expression on these vascular cells.
Patients with cardiovascular involvement were reported, without consistent histological evidence. Only one case of cardiac tamponade in a 47-year-old man with SARS-CoV-2 infected without CV risk has been reported in the literature as a complication of myocarditis and pericarditis. The causes of hydropericardium and cardiac tamponade also include infectious and inflammatory causes (15%) and mechanical complications of MI (12%). Patients who died of complications of COVID-19 are elderly and often have comorbidity due to CVD.

Myocarditis, with the presence of inflammatory infiltrates in the myocardial interstitium and with the structural damage validated by the laboratory markers of damage and cardiac necrosis, can be a secondary complication of the immune response and not of the direct action of the virus on cardiomyocytes. To date, there is no evidence of RNA coronaviruses in the heart.

Considering the reported presence of ACE2 in different cell types and also in the heart, a hematogenous diffusion of the pathogen and a similar interaction as happens in the lung, the hypothesis remains that the SARS-CoV-2 action on the heart in old people is mediated by systemic imbalance caused by the alteration of the functioning of the RAAS on comorbidity background.

CMR availability issues, coupled with the potential for in-hospital spread of the virus related to the logistics of performing such tests, hamper the use of this valuable imaging modality. In this context, endomyocardial biopsy could provide key insights, whereas bedside echocardiography could give information on LV function.

Certain ethnic groups may be disproportionately affected by SARS-CoV-2. COVID-19 death rates were shown to be higher among the African-American population than other ethnicities in many American states. Although this may partially be explained by the greater number of CV risk factors or the genetic predisposition to poorer cardiac outcomes, healthcare disparities cannot be dismissed. Bias in the health and care provisions may be the driving force behind disproportionate suffering in minorities. Arrhythmias could occur in the context of myocarditis.

Peretto et al. reported in a recent study that 78.7% of myocarditis patients exhibited some form of ventricular arrhythmia. The characteristics of arrhythmias differ between active and healed myocarditis, suggesting that the pathophysiology is dependent on the stage of myocardial injury.

ARRHYTHMIAS

Arrhythmia has been recognized as one of the possible clinical manifestations of COVID-19 disease. One observational study of the clinical characteristics of COVID-19 patients in Hubei, China, reported a 7.3% incidence of palpitations among 137 patients. Wang et al. reported that arrhythmia was a cause of ICU transfer in 44.4% of COVID-19 patients. Caution is encouraged when interpreting these data, as the sample size tends to be small and hence prone to overestimation.

The exact nature of arrhythmias was not usually reported, so assessing whether the arrhythmias are secondary to other conditions such as electrolyte imbalance or pre-existing arrhythmias is difficult. Therefore, the actual prevalence of arrhythmias in COVID-19 patients remains unknown. Nevertheless, arrhythmias could occur in the context of myocarditis.

However, the largest observational study from China, with 1099 patients from 552 hospitals, did not report any arrhythmia.

Goyal et al. in a recent retrospective case series on 393 consecutive patients with COVID-19 in two hospitals in New York City found that patients who received mechanical ventilation were more likely to have atrial arrhythmias (18.5% vs. 1.9%). Arrhythmia was seen in 7.4% of the entire cohort, with higher rates in patients receiving ICU care (18.5%) as compared to non-ICU care (1.8%). Arrhythmias may be induced by the presence of acidosis and metabolic disturbances, as seen in critical illness with multigorgan dysfunction or catecholaminergic pressor infusion for hypotension and shock. Finally, QT-prolonging agents given to some COVID-19 patients may increase the susceptibility to arrhythmia as discussed below.

In 136 COVID-19 patients who experienced in-hospital cardiac arrest, Shao et al. revealed that the most common initial rhythm was asystole in 89.7% of cases. Pulseless electrical activity was found in 4.4%, whereas a shockable rhythm was identified in only 5.9% of patients. This was similar to another study where they found that, among patients who suffered a cardiac arrest, the predominant rhythm was asystole/pulseless electrical activity (94%), followed by shockable ventricular tachycardia/fibrillation (6%).

Du et al. reported that arrhythmia occurred in 51 of 85 fatal cases of COVID-19 from Wuhan, and two patients died of malignant arrhythmias. Cardiac arrest-triggered sudden death appears to be a common cause of death in patients with COVID-19. In 85 fatal cases of COVID-19, cardiac arrest is the direct cause of death of seven patients. Moreover, patients with elevated TnT experienced higher risk of ventricular arrhythmias (17.3% in high TnT group vs. 1.5% in normal TnT group). In addition to acquired arrhythmia, patients with inherited arrhythmia syndromes, including long and short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, are believed to be more susceptible to pro-arrhythmic effects of SARS-CoV-2 such as stress, fever, use of antiviral drugs, and electrolyte disturbance.
The possible pathophysiology of arrhythmias in SARS-CoV-2 includes (1) direct injury to cardiomyocytes disrupting the plasma membrane and electrical conduction; (2) infection of the pericardium causing massive edema; (3) ischemia from microvascular disease due to possible infection of the pericytes; (4) re-entrant arrhythmias due to myocardial fibrosis or scars; and (5) pro-inflammatory cytokines predisposing to arrhythmogenicity. Scenarios 1, 2, and 3 could occur in the acute setting, whereas scenarios 4 and 5 occur in chronic or healed myocarditis.

In scenario 5, pro-inflammatory cytokines (e.g., IL-6) might cause displacement of plakoglobin, a desmosomal protein, from the cardiomyocyte membrane. This could be arrhythmogenic as inadequate cell-to-cell adherence is postulated to damage the cell membrane, leading to cardiac cell death and fibrofatty replacement. Moreover, reduced surface expression of desmosomal proteins is a known etiology of arrhythmogenic cardiomyopathies.

Substantial evidence now suggests an increase in the serum IL-6 in COVID-19 patients, especially in those with severe presentations. Therefore, it is plausible that SARS-CoV-2 infection precipitates arrhythmias in patients with a genetic predisposition. Clinicians should be vigilant for arrhythmias, especially in areas where both the COVID-19 burden and the arrhythmogenic cardiomyopathy prevalence are high, such as the North-Eastern (Veneto) region of Italy.

While there is a paucity of literature detailing COVID-19–related arrhythmogenic complications, there are reports of ventricular tachycardia and ventricular fibrillation as the late manifestations of COVID-19. An early case series from China reports a 16.7% incidence of arrhythmia but did not specify the cause or type. A later report found a 5.9% incidence of malignant arrhythmias, with a significantly greater incidence in those with evidence of myocardial injury (17.3% vs. 1.5%). This perhaps suggests that myocardial injury may serve as a substrate for subsequent cardiac arrhythmias, and frequent arrhythmia should heighten suspicion for a myocardial inflammatory process. This phenomenon may, in part, account for the reported increase in out-of-hospital arrests noticed during the COVID-19 pandemic period. Notably, however, analysis of in-hospital arrests in COVID-19 patients seem to be rarely from shockable rhythms (89.7% asystole, 4.4% pulseless electrical activity, and 5.9% shockable rhythm).

Arrhythmias could also be precipitated by electrolyte imbalances, which have been observed in populations with COVID-19. The interaction of SARS-CoV-2 with the RAAS has caused increasing concerns about sodium and potassium disorders, which may increase vulnerability to various tachyarrhythmias. In addition, hypoxia, a common clinical manifestation of severe COVID-19, has been associated with alterations of cardiomyocyte gap junctions which could contribute to the development of atrial arrhythmias, especially atrial fibrillation.

SARS-CoV-2 invades cells by binding to ACE2 receptors, which can enhance urinary potassium excretion due to increased availability of angiotensin II. Treatment of arrhythmias should focus on addressing all reversible causes, especially electrolyte abnormalities, and follow standard guidelines for the management of arrhythmias. In the setting of frequent and uncontrolled ventricular arrhythmia not responding to antiarrhythmic therapy, transvenous pacemaker insertion and/or mechanical circulatory support should be considered.

Guo et al. reported sustained ventricular tachycardia or ventricular fibrillation in 5.9% of patients admitted to the ICU (44.4%) with a significantly higher incidence in patients with elevated TnT.

Arrhythmias can also be induced by novel medical therapies for COVID-19; despite the unclear data about the effectiveness of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of COVID-19, the Food and Drug Administration of the United States of America issued an emergency authorization for their use under determined circumstances in patients with COVID-19. Both agents may increase the risk for torsades de pointes or other ventricular arrhythmias via QTc prolongation and could also lead to advanced types of atrioventricular (AV) block.

To the best of our knowledge, there are no specific reports on occurrence of bradycardia in COVID-19 infection. However, an experimental study has shown that coronavirus-infected rabbits have ECG abnormalities including second-degree AV block secondary to myocarditis and HF. In severely ill patients admitted in the ICU due to COVID-19, transient bradycardia and asystole may occur due to patient turning for prone position, intubation, or trachea suction that likely occur due to the temporary increased vagal tone.

Currently, there are no special considerations or treatment algorithms specifically for arrhythmias related to COVID-19. The first principle for atrial arrhythmias presenting with rapid ventricular response (RVR) in the setting of COVID-19 is that there is no need to acutely lower heart rates in these patients if they are hemodynamically stable. Easing their respiratory distress with oxygen and treating their fever may decrease some of their drive for RVR. Furthermore, it is recommended that patients be initiated on appropriate anticoagulation in the absence of coagulopathy, bleeding, or other contraindications.

To avoid iatrogenic hypotension, bradycardia, or decompensation of systolic HF, it is recommended to...
avoid intravenous calcium channel blockers. If patients are hemodynamically stable and without evidence of HF, oral β-blockers can be slowly introduced. If there is concern for acute HF, hypotension, or other hemodynamic derangements, amiodarone is the antiarrhythmic of choice. Patients presenting with unstable atrial arrhythmias or malignant ventricular arrhythmias should be treated as per advanced cardiac life support guidelines with immediate cardiology consultation.

**ACUTE MYOCARDIAL INJURY**

Myocardial injury is defined as an elevation of high-sensitivity cTnI above 99th percentile upper reference limit.

Possible pathophysiological mechanisms of myocardial injury are:

1. Direct myocardial injury: It is postulated that SARS-CoV-2 enters human cells by binding to ACE2, leading to acute injury in tissues where it is expressed. The virus has still not been isolated in the cardiac tissue; however, it is believed to be associated with cardiomyocytes degeneration, inflammatory infiltrates in the myocardial interstitium, and microthrombi formation.

2. Systemic inflammation: Cytokine storm observed in COVID-19 patients can result in injury to multiple organs, leading to multiorgan failure. Systemic inflammation is a well-known factor of plaque instability, being able to result in acute MI. Corroborating the inflammatory hypothesis, the plasma IL-6 seems to be consistently increased in patients with COVID-19 and cardiac injury, often evolving in life-threatening arrhythmias and/or fulminant myocarditis.

3. Hypoxia: Increased metabolic demand due to the systemic infection and hypoxia caused by respiratory distress can impair myocardial oxygen demand–supply.

The incidence of acute myocardial cardiac injury in COVID-19 patients, previously reported to be 7.2%, has recently been found to be much higher in two different studies, with an incidence of 19.7% and 27.8%, respectively. These studies also demonstrated that cardiac injury was independently associated with an increased risk of mortality and that COVID-19 patients with cardiac injury presented with more severe acute illness, worse radiographic findings, and a higher risk for invasive ventilation.

A recent meta-analysis also suggested that there may be a correlation between the values of cTnI and the severity of clinical presentation; cTnI values were found to be significantly increased in COVID-19 patients with severe disease compared to mild–moderate cases. These findings are compatible with acute myocardial injury being predictive of negative outcomes in COVID-19 patients.

Elevated troponin levels have been observed between 7% and 27.8% of COVID-19 patients. An increasing number of reports have described cardiac injury and absence of coronary obstruction, during severe COVID-19 infection.

Two single-center studies described this clinical finding. In a retrospective cohort of 416 patients with laboratory-confirmed COVID-19, Shi et al. reported that 19.7% had evidence of myocardial injury as defined by an hsTnI value greater than the 99th percentile reference limit. In-hospital mortality was 51.2% among patients with myocardial injury compared with 4.5% among patients without myocardial injury. Furthermore, the mortality rate was associated with the magnitude of troponin elevation. Similarly, Guo et al. observed that among 187 patients hospitalized with COVID-19, 52 (27.8%) exhibited myocardial injury as demonstrated by the elevation of cTnT.

In-hospital mortality was more than 6-fold higher in patients with elevated cTnT levels than in patients with normal cTnT levels (59.6% vs. 8.9%). Moreover, patients with underlying CVD and increased cTnT levels comprised a subgroup with even higher mortality (69.4%). In contrast, patients with underlying CVD without cTnT elevation experienced a more favorable prognosis (mortality 13.3%), albeit still higher than patients without CVD or elevated cTnT (mortality 7.6%). In this study, cTnT levels were statistically significantly correlated with the blood concentrations of CRP and NT-proBNP, suggesting a link to the degree of systemic inflammation and myocardial wall stress. In both studies, patients with evidence of myocardial injury were also older with a higher prevalence of coronary heart disease, cerebrovascular disease, chronic HF, chronic renal failure, chronic obstructive pulmonary disease, HTN, and diabetes.

Elevated troponin levels also have a strong prognostic implication in those with COVID-19 disease. Several studies have shown that those with elevated troponin levels at baseline have a greater risk of having a severe disease, increased ICU admissions, and significantly higher mortality. In a cohort study, the presence of elevated troponin levels was second to the presence of ARDS in the strength of association with mortality.

Guo et al., in a single-center retrospective analysis of 187 COVID-19 patients, studied the relationship of baseline troponin levels and other comorbidities with mortality. They reported that the risk of death can be stratified according to the presence of elevated troponin and/or history of CVD. The risk of death in these patients increased linearly, with 7.62% of those dying with no history of CVD compared with
13.3% of those with presence of only history of CVD, 37.5% in those with presence of elevated troponin levels only, and 69.4% in those with both elevated troponin levels and history of CVD. Notably, elevated troponin level carried a strong prognostic value even in the absence of CVD history. In addition, the authors reported that in survivors, during the hospitalization period, the troponin levels remained stable and within normal limits. On the other hand, nonsurvivors showed a trend of gradual and progressive increase in the troponin levels. This suggests that troponin elevation may reflect progression of the disease to a severe stage,[10] notably through a continual inflammatory surge.

If troponin elevation occurs in the absence of clinical symptoms, ECG changes, and other indications, extensive investigations, such as echocardiography and coronary angiography, are not recommended routinely to exclude acute coronary event. Similarly, although it is crucial to ensure adherence to long-term prescribed CV therapies, it is unclear whether isolated elevation of troponin warrants any CV therapy.

**HEART FAILURE**

HF and cardiogenic shock appear to be the important causes of morbidity and mortality in COVID-19. The development of new HF is common in patients with COVID-19 disease.

In a study of 191 patients with confirmed COVID-19 from two Chinese hospitals, 23% of patients had a clinical diagnosis of HF.[11] Of the patients who died during the study, 52% had HF versus 12% with HF were among the survivors.[12] Interestingly, the development of HF syndrome was more commonly observed than acute kidney injury. In another retrospective case series of 150 patients with COVID-19 from two Chinese institutions, 33% of deaths were attributed to respiratory failure with myocardial damage or HF, with an additional 7% reported as HF without respiratory failure.[13] In a clinical review of these deaths, the researchers suggested that fulminant myocarditis may have been the etiology of the HF; however, no additional diagnostic details were included.

Arentz et al.[14] in a small US case series, identified seven out of 21 critically ill patients (33%) who developed cardiomyopathies during the course of their ICU stay.[15] The exact etiology of ventricular failure in COVID-19 remains unknown. Patients developed dilated cardiomyopathy, characterized by globally decreased LV systolic function, clinical signs of cardiogenic shock, elevated CK or TnI levels, or hypoxemia, without a history of systolic dysfunction.[16]

Chen et al. from China reported HF as a complication in 24.4% of COVID-19 population, using age-related amino-terminal pro-BNP cut-offs, which yielded 90% sensitivity and 84% specificity for acute HF.[17] There was significant difference in the prevalence of HF between COVID-19 survivors and nonsurvivors (3.2% vs. 49.4%).[18] Among those with HF, nearly half did not have a previous history of HTN or CVD.[18] In a meta-analysis of 43 studies involving 3600 patients, the prevalence of HF as a complication was 17.1% among critically ill patients compared to 1.9% among noncritically ill patients.[19]

HF is characterized by decreased LVEF and drastically elevated NT-proBNP. Guo et al.[20] reported that patients with elevated TnT have a higher level of cardiac biomarkers and NT-proBNP.[21] Moreover, a tight correlation was identified between NT-proBNP and TnT levels, indicating that patients with myocardial injury are at higher risks of cardiac dysfunction or HF.[22] Although COVID-19 patients often display comorbidities affecting cardiac diastolic function including diabetes, obesity, and HTN, few studies have revealed a relationship between HF with preserved ejection fraction (HFpEF) and COVID-19.

Sinkey et al.[23] reported a case of a postpartum patient with COVID-19 and preeclampsia who developed HFpEF.[24] Notably, loss of ACE2, the receptor for SARS-CoV-2, increases the pro-inflammatory macrophage phenotype in the heart from patients with HFpEF.[25] Further study is warranted to explore the precise interplay between SARS-CoV-2 and HFpEF. HF in COVID-19 patients is attributable to myocardial injury, systemic inflammatory response, pulmonary HTN and ARDS, renal dysfunction, retention of water and sodium, and imbalance of myocardial oxygen demand and supply.

Some experts have speculated that HF syndrome seen in COVID-19 is mediated predominantly through systemic inflammation and cytokine storm.[26] This theory is grounded in the reports from several studies that have shown markedly elevated inflammatory markers including IL-6, D-dimer, and lactate dehydrogenase in patients with severe COVID-19.[27,28]

Higher levels of the serum BNP have been shown to correlate with cardiogenic PE in ARDS.[29] Interestingly, patients with COVID-19 may have high levels of BNP in the absence of significant ventricular dysfunction.[30,31] Still, the presence of elevated cardiac biomarkers, particularly troponin, should raise clinical suspicion of HF. Interpretation of cardiac biomarkers does, however, present significant challenges as there are multiple mechanisms of cardiac injury.

HF could be attributable to either the exacerbation of underlying CVD or the new onset of cardiomyopathy (particularly, myocarditis or stress cardiomyopathy) in patients with COVID-19. Isolated right HF can be observed in the presence of pulmonary HTN in the setting of severe ARDS or PE.[32] Older adults with CVD often have LV hypertrophy and diastolic dysfunction. Thus, these patients may be prone to develop pulmonary edema when they are given...
Venovenous ECMO is a treatment for COVID-19. A pooled analysis of early reports suggested that ECMO could be beneficial, particularly when considering mechanical respiratory support. However, in 12 critically ill COVID-19 patients requiring ECMO, Zeng et al. found that nearly half of them died of septic shock and multiorgan failure. Duration of ECMO support ranged from 3 to 28 days. A pooled analysis of early reports including 234 ARDS patients revealed that only 7.2% received ECMO. The mortality rate was 94.1% in patients who received ECMO and 70.9% in patients on conventional therapy.

The pooled effect of ECMO versus conventional therapy on mortality was neutral. The Extracorporeal Life Support Organization recommends the use of ECMO only in expert centers for patients with severe ARDS after multidisciplinary team discussion on a case-by-case basis.

ECMO can be considered futile, and the patient can be returned to conventional management, if no lung or cardiac recovery is observed after 21 days. Venovenous ECMO is a treatment for refractory respiratory failure, and venoarterial ECMO may be used when the patient is also in the need of circulatory support. However, it is unknown whether particular populations of patients respond better to therapy with ECMO than others and what criteria are the best used for careful selection of patients who are most likely to benefit in the present resource-constrained environment. In addition, the time course for possible recovery and successful decannulation strategies from ECMO have not been well described at this time.

ADDITIONAL VASCULAR COMPLICATIONS OF COVID-19 DISEASE

In autopsy evaluations of three patients who died of SARS-CoV-1, microthromboses and macrothromboses were observed. A prominent finding of SARS-CoV-2 is disarray of the coagulation and fibrinolytic system, with > 70% of nonsurvivors having most criteria fulfilling disseminated intravascular coagulation (DIC). It may be hypothesized that myocardial injury is a result of microthrombus formation in the myocardial vasculature in the setting of a hypercoagulable state like DIC.

Patients suffering from COVID-19 infection are at risk for venous thromboembolic (VTE) and arterial thromboembolic events, especially in the setting of DIC. Infections and sepsis are the leading causes of DIC, in general. The exact mechanism of DIC in the setting of sepsis and ARDS is complex but is generally thought to be related to an immune-mediated exhaustion of the coagulation and fibrinolytic systems promoting bleeding and thrombosis in the same patient. Endothelial injury and inflammatory cytokines, such as IL-6 and
TNF-a, upregulate tissue factor expression, driving a prothrombotic state.\cite{125}

Dysregulation of antithrombin III, plasminogen activator inhibitor type 1, and protein C in the setting of significant inflammation and sepsis promotes an anticoagulated state.\cite{126} Furthermore, platelet activation also ensues in the context of sepsis and inflammation, further tipping the fine balance of the coagulation system.\cite{127} It is postulated that the immune activation seen in severe COVID-19 infection is likely sufficient to trigger DIC, microvascular dysfunction, and myocardial injury.

Lodigiani et al.\cite{128} from Italy described a 7.7% incidence of at least one thromboembolic event for hospitalized patients with COVID-19.\cite{129} This rate can be as high as 31% in those requiring ICU-level care.\cite{130} Further, acute arterial thrombotic events other than ACS, such as cerebrovascular accident or systemic thrombosis, have been observed in COVID-19 patients with no or few predisposing factors.\cite{128-130}

Although the mechanism of coagulopathy is unclear, it is likely multifactorial with critical illness, inflammation, and endothelial dysfunction contributing to coagulopathy. It is evident that COVID-19 patients develop some degree of abnormal coagulation parameters.\cite{10,105} It has been reported from China that elevated levels of D-dimer (>1 μg/L) and fibrin degradation products are strongly associated with in-hospital death.\cite{105}

Thromboembolic anomalies and coagulopathy, including VTE, PE, and DIC, are believed to be highly prevalent in COVID-19 patients. For example, a mass of PE was noted in COVID-19 patients, and the prevalence of PE was twice higher in ICU COVID-19 as all ICU or influenza ICU patients.\cite{131}

Retrospective studies have identified PE as the most common thrombotic event.\cite{128,129} Those with thrombotic complications have a higher risk of death and higher D-dimer levels.\cite{128,129,132} Chen et al.\cite{132} reported median D-dimer level of 11.07 μg/ml compared to 2.44 μg/ml in those without PE.\cite{132} Wichmann et al.\cite{133} in a prospective cohort study examining 12 postmortem COVID-19 patient autopsy found deep venous thrombosis in 58% and PE in 33%.\cite{133}

Thromboembolic events, particularly PE, may contribute to the rate of cardiac injury detected in severe COVID-19 disease as RV strain may lead to the elevation in cardiac biomarkers. Even in the absence of significant clot burden, PE may significantly impair RV performance, especially in the setting of high RV afterload that is characteristic of ARDS.\cite{134} In severe cases, cor pulmonale can develop, which may contribute to the mixed shock or sudden cardiac arrest observed in severe COVID-19 disease.

CONCLUSION
The COVID-19 due to its greater transmissibility has posed a pandemic, representing the most important public health crisis of the current era. Patients having a history of CVD are especially vulnerable to COVID-19 and are often afflicted with severe forms of the infection. CV manifestations of COVID-19 can be either primary/direct or secondary/indirect. Primary cardiac manifestations of COVID-19 include ACS, myocarditis, and arrhythmias.

Secondary cardiac involvement is usually due to a systemic inflammatory syndrome and can manifest as acute myocardial injury/biomarker elevation and/or HF, PE, and cardiogenic shock. Management of CV manifestations of COVID-19 has to be decided case by case as one size does not fit all, and a close collaboration of different teams is required to treat very sick patients.

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