

# Cardiovascular Complications of COVID-19

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## Abstract

Coronavirus disease 19 (COVID-19) has rapidly expanded to a global pandemic, resulting in significant morbidity and mortality. Even though predictors of infection remain unclear, age and preexisting cardiovascular conditions have been clearly identified as predictors of adverse outcomes and higher fatality rates. Since the virus infects host cells through angiotensin-converting enzyme 2 receptors, a key player in the renin-angiotensin-aldosterone system, the interaction between the cardiovascular system and the progression of COVID-19 is nowadays a focus of huge interest. In this review, the authors analyze the available and very recent evidence on the risk factors and mechanisms of the most relevant cardiovascular complications associated with COVID-19, including acute cardiac injury, myocarditis, stress-cardiomyopathy, ischemic myocardial injury, cytokine release syndrome, thrombotic disease, cardiac arrhythmias, heart failure, and cardiogenic shock. Finally, we discuss the cardiovascular impact of the therapies under investigation for COVID-19 treatment.

**Keywords:** Acute cardiac injury, arrhythmia, cardiovascular diseases, coronavirus disease-19, myocarditis, thromboembolic complications

## INTRODUCTION

At the beginning of 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was identified as the cause of an outbreak of viral pneumonia in Hubei China. Later on, 11<sup>th</sup> March, the World Health Organization declared Coronavirus Disease 19 (COVID-19) a global pandemic. As of the end of August, >25 million cases were confirmed, and a death toll >800,000 has been documented worldwide.<sup>[1]</sup>

COVID-19 most common manifestations are fever and dry cough.<sup>[2,3]</sup> However, other symptoms such as fatigue, anorexia, dyspnea, myalgia, and gastrointestinal symptoms have been reported.<sup>[2,3]</sup> In atypical cases, the cardiovascular symptoms may be the first manifestation, making the diagnosis more challenging and delaying the recognition of the disease.<sup>[4]</sup> Usually, symptoms develop 2–14 days after exposure, with a mean incubation period of 4 days.<sup>[3]</sup>

The disease has a heterogeneous clinical course, ranging from asymptomatic to critical state. In the largest cohort published so far, with over 44,000 people, 81% presented mild-to-moderate disease, 14% severe, and 5% critical.<sup>[5]</sup> Mild COVID-19

manifests as a common viral respiratory infection associated with lymphopenia, whereas severe disease may present as interstitial pneumonia complicated with acute respiratory distress syndrome. In some patients, massive cytokine release leads to a pro-inflammatory state with multiorgan failure, often times fatal. In a study with 1099 patients, 5% were admitted to the intensive care unit (ICU), and 2.3% required invasive mechanical ventilation.<sup>[3]</sup> The fatality rate varies among series, ranging from 2% to 4% in the overall population, to 40% in ICU patients.<sup>[5]</sup>

The most frequent complications are sepsis, respiratory failure, acute heart failure, and septic shock. Unsurprisingly, complication rates are higher in ICU patients and among nonsurvivors.<sup>[2]</sup> Similarly, the occurrence of co-infection was statistically associated with mortality (16% vs. 1%,  $P=0.001$ ).<sup>[6]</sup>

Cardiovascular complications during respiratory viral

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infections, such as influenza or respiratory syncytial virus infection, have been well recognized. Similar to SARS-CoV2 other two highly pathogenic coronavirus, SARS-CoV and Middle East Respiratory Syndrome, cause acute severe infections with a high burden of cardiovascular complications.

In this review, we will briefly summarize the impact of SARS-CoV2 on the cardiovascular system.

## CLINICAL COURSE OF CORONAVIRUS DISEASE 19 AND PREDICTORS OF SEVERITY

Several case series have allowed identifying predictors of severity in individuals infected with SARS-CoV2, but the evidence on risk factors for infection persists extremely limited.

Regarding disease severity in patients infected with SARS-CoV2, age is the strongest risk factor for adverse outcomes and mortality.<sup>[2,7,8]</sup> In a study with 52 critically-ill patients, mortality was strongly associated with older age ( $P < 0.001$ ).<sup>[6]</sup> A mortality rate as high as 14.8% was reported in patients over 80 years old.<sup>[9]</sup> In contrast, there seems to be no association with gender.<sup>[2,6,8]</sup>

Cardiovascular diseases (CVD) are the most commonly reported comorbidities and are more frequent in patients with severe forms of COVID-19.<sup>[10]</sup> Whether CVD also predispose to SARS-CoV2 infection needs further investigation. In a cohort with 5700 patients, the most prevalent comorbidities were hypertension (56.6%), diabetes (33.8%), obesity (41.7%), coronary heart disease (11.1%), and congestive heart failure (6%–9%).<sup>[11]</sup> Considering hypertension, initial studies reported a frequency within the expected prevalence for the overall population. For instance, a Chinese cohort with 1099 COVID-19 patients showed that 15% of patients were hypertensive,<sup>[3]</sup> in line with the estimated prevalence of hypertension in China, which is 23.2%.<sup>[12]</sup> In contrast, other study documented higher prevalence of hypertension and CVD in patients with COVID-19 than in controls.<sup>[13]</sup> Similarly, among 12,594 patients tested for COVID-19, pre-existing hypertension was reported in 39.6% of the overall population as opposed to 59.1% in SARS-CoV2-positive patients.<sup>[14]</sup>

There is consistent evidence that CVD burden is a significant predictor of COVID-19 severity, being more prevalent in patients admitted to the ICU, requiring mechanical ventilation or nonsurvivors.<sup>[3,6,7,10]</sup> In a study with critically ill patients requiring ICU admission, 42.9% had previous congestive heart failure diagnosis.<sup>[15]</sup> According to the report from the Chinese Center for Disease Control and Prevention, the overall COVID-19 mortality is estimated in 2.3%, reaching rates as high as 10.5% in patients with preexisting CVD, 6% in patients with hypertension, and 7.3% in patients with diabetes.<sup>[5]</sup> Nevertheless, aging associates closely with these comorbidities and it is likely to be a confounding factor for disease severity.

Considering obesity, a strong association between higher body mass index (BMI) and COVID-19 severity has been reported

with increased risk of hospitalization (odds ratio [OR] 6.2 for BMI  $>40$  kg/m<sup>2</sup>),<sup>[16]</sup> admission to the ICU (OR 3.5 for BMI  $>35$  kg/m<sup>2</sup>)<sup>[17]</sup> and mortality ( $P = 0.005$ ).<sup>[18]</sup> Moreover, obesity may predispose to infection. A study with  $>3700$  patients detected a significantly higher risk of COVID-19 in obese patients after adjusting for comorbidities and confounding factors.<sup>[19]</sup> Interestingly, the correlation between BMI and both the risk of infection and disease severity is increased in younger patients.<sup>[17-19]</sup>

## MECHANISMS OF CARDIOVASCULAR INVOLVEMENT IN CORONAVIRUS DISEASE 19

Current evidence supports an overlap between pathways leading to CVD and immune dysregulation. Aging is associated with immune dysfunction, and it is the single strongest risk factor for CVD. Therefore, CVD burden is considered as a marker of immune dysregulation, strengthened by the presence of other comorbidities such as diabetes or dyslipidemia. This may explain the increased susceptibility to COVID-19 severe infection in patients with preestablished CVD. Even though a higher incidence of cardiovascular complications is seen in patients with previous CVD, the virus itself may induce cardiovascular damage. The exact pathophysiological mechanism is still unknown, and multiple pathological pathways may be implicated.

SARS-CoV2 enters the host cell by binding its spike protein to the angiotensin-converting enzyme 2 (ACE2), a transmembrane protein expressed in multiple cell types. Despite COVID-19 tropism for the respiratory system, multiorgan failure has been reported. This phenomenon may be partially explained by the tissue distribution of ACE2, a ubiquitous membrane-bound aminopeptidase with a significant presence in type II alveolar epithelial cells, myocardial, and endothelial cells. Endocytosis of SARS-Cov2-ACE2 complexes allows virus access to the intracellular compartment and simultaneously decreases the ACE2 abundance at the cell surface, decreasing the ACE2 enzymatic activity. ACE2 is the main counter mechanism of angiotensin-2, by inducing its cleavage into angiotensin 1–7 and consequently attenuating its effects on vasoconstriction, sodium retention, fibrosis, and inflammation.<sup>[20]</sup> Furthermore, angiotensin 1–7 has specific anti-inflammatory and vasodilator properties that protect the angiotensin-2-producing tissues from excessive local action.<sup>[21]</sup> It has been proposed that the downregulation of ACE2 at pulmonary endothelial cells induced by the SARS-CoV2 internalization causes a local angiotensin 1–7/angiotensin-2 imbalance and that unimpaired angiotensin-2 increases lung vascular permeability causing lung edema and respiratory failure.<sup>[22,23]</sup> In a cohort of 12 COVID-19 patients, angiotensin 2 serum levels were markedly elevated and correlated with viral titers with a tendency to worsened the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, reinforcing that imbalanced renin-angiotensin-aldosterone system (RAAS) activation may be a key factor in disease severity.<sup>[24]</sup> Another study described high incidence of hypokalemia in COVID-19 patients and

reported that the degree of hypokalemia was directly correlated with disease severity.<sup>[25]</sup> This ionic disturbance was not clearly related to gastrointestinal loss and seemed to be due to increased kaliuresis, suggesting that the upregulation of RAAS may be critical in the severe forms of COVID-19. SARS-CoV also enters cardiac host cells through ACE2 binding. In a postmortem study, viral genome was detected in 35% of autopsied hearts with co-existent inflammation, pathological hypertrophy and decreased ACE2 levels.<sup>[26]</sup> Patients with cardiac involvement presented a more aggressive disease course and higher mortality.<sup>[26]</sup> These findings provide a direct pathway of viral-induced cardiomyocyte injury.

Endothelial inflammation is a key factor for microcirculatory dysfunction and associated end-organ lesion. In COVID-19, two mechanisms may be expected: (1) direct endothelial infection with viral particles causing endothelitis;<sup>[27,28]</sup> and (2) systemic inflammation, enhancing coagulation and platelet activation, contributing to endothelial dysfunction and predisposing to thrombotic events.<sup>[29]</sup> In fact, a report of lung autopsies in COVID-19 patients showed a significant increase in pulmonary angiogenesis and microvascular thrombosis when compared to influenza patients.<sup>[28]</sup>

Finally, infectious diseases induce hypoxia and increased cardiometabolic demand, reducing oxygen supply and favoring myocardial ischemia. Increased right ventricular (RV) overload in the context of hypoxia, metabolic acidosis, and mechanical invasive ventilation may also trigger ischemia.<sup>[30]</sup> Atherosclerosis is a chronic inflammatory state, and the progression of disease has been described in the set of systemic infections. In acute infections, abrupt inflammatory changes in coronary arteries may also induce plaque destabilization and rupture, culminating in acute coronary events.<sup>[30]</sup>

## HYPERTENSION AND RENIN-ANGIOTENSIN-ALDOSTERONE ANTAGONISTS

Taking into account that SARS-CoV2 uses the ACE2 receptor to invade host cells and recognizing that ACE2 is a key player in the RAAS, it is tempting to hypothesize that RAAS blockers may impact the propensity to SARS-CoV2 infection or to modulate the progression and severity of COVID-19. In this context, it is of paramount relevance to discuss the available evidence, aiming to clarify if there exists any association between RAAS antagonists' treatment and COVID-19 and to evaluate if such putative interaction is favorable or deleterious.

As SARS-CoV2 uses ACE2 to facilitate cell entry, it has been postulated that patients taking RAAS blockers would present increased susceptibility to infection if the chronic use of such drugs would induce ACE2 overexpression. The concept of ACE2 up-regulation with RAAS blockers resulted from animal studies.<sup>[31]</sup> However, proof of the direct effect of RAAS inhibition on lung-specific ACE2 levels is missing. More importantly, the effect found on preclinical studies may

not readily translate to humans, as results from clinical studies regarding the effect of RAAS inhibition in ACE2 levels are conflicting.<sup>[20]</sup> Accordingly, large observational studies did not find an association between RAAS inhibitors and increased risk of infection or adverse outcomes.<sup>[13,14]</sup> Conversely, a positive association between COVID-19 and the use of diuretic therapy was found.<sup>[13]</sup> These results may not suggest a pharmacological interaction, but rather an increased susceptibility in patients with serious comorbidities requiring diuretics, such as heart failure or chronic kidney disease.<sup>[13]</sup>

Therefore, scientific societies have urged not to discontinue RAAS blockers in stable patients with COVID-19, as their benefit on myocardial and kidney function is well established and withdrawal may trigger decompensation, particularly in high-risk patients.<sup>[32]</sup>

Recently, the concept that enhanced RAAS activity may play a key role in determining disease severity has risen the interest in counteracting Ang-2 activity. In animal models of severe viral infection, it was shown that RAAS blocker treatment may reduce the extent of lung injury.<sup>[33-35]</sup> Relevantly, losartan (NCT04311177 and NCT04312009) and exogenous ECA2 administration (NCT04287686) are being evaluated in ongoing clinical trials.

## ACUTE CARDIAC INJURY

Acute cardiac injury is the most common cardiovascular event reported in COVID-19, with rates ranging from 7.2% to 36%.<sup>[36,37]</sup> Myocardial injury in patients with COVID-19 could be due to plaque rupture, cytokine storm, hypoxic injury, coronary spasm, microthrombi, direct endothelial, or vascular injury. The criteria applied for diagnosis differed among cohorts, while the majority considered only a rise in serum troponin (Tn) above the upper threshold, others also included electro or echocardiography changes. The etiology of the underlying myocardial injury was not clarified in most studies. A wide range of mechanisms may mediate myocardial injury besides acute coronary syndrome and should be considered in the differential diagnosis, such as myocarditis, stress cardiomyopathy, cytokine release syndrome, acute heart failure, arrhythmias, renal impairment, and toxic injury.<sup>[38]</sup>

Acute cardiac injury has been consistently associated with worse clinical outcomes in COVID-19, being 13 times more frequent in patients with severe disease.<sup>[10]</sup> Recent cohorts reported a positive correlation between acute cardiac injury and elevation of inflammatory biomarkers, respiratory failure requiring mechanical ventilation, renal failure, and coagulation disorders.<sup>[37,39,40]</sup> Moreover, in a cohort with 3096 individuals, it was recognized as an independent risk factor for in-hospital mortality after adjusting for age, comorbidities, and disease severity ( $P < 0.001$ ). The fatality risk was directly correlated with the magnitude of Tn elevation.<sup>[37]</sup>

Older individuals and patients with preexisting CVD are more likely to suffer myocardial injury.<sup>[37,39]</sup> Guo *et al.* reported the highest mortality rates in patients with preexisting CVD who

developed myocardial injury.<sup>[39]</sup> Interestingly, patients with CVD but without Tn rise presented more favorable outcome than individuals without CVD who developed myocardial injury (mortality, 13.3% vs. 37.5%). In addition, Tn rise, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and the incidence of malignant arrhythmias were strongly associated, and both the magnitude of Tn and NT-proBNP elevation and their dynamic changes during hospitalization were correlated with mortality.<sup>[39]</sup> These results suggest that myocardial injury plays a critical role in fatality, eventually greater than previous CVD.

## ISCHEMIC MYOCARDIAL INJURY

Viral infections may be a trigger for plaque disruption, as reported by Kwong *et al.*, who detected an incidence ratio of acute type 1 myocardial infarction (MI) after influenza infection of 6.05 (95% confidence interval [CI]: 3.86–9.50) when compared to healthy controls.<sup>[40]</sup> However, it is critical to notice that myocardial necrosis in the setting of viral infections is more frequently due to type 2 mechanisms, justifying the need for therapeutic strategies completely different from those used in type 1 MI.<sup>[30]</sup> In addition, SARS-CoV2 tropism for endothelial cells induces microvascular dysfunction, and therefore, MI with nonobstructive coronary arteries may occur. This reinforces the necessity of an individualized invasive strategy, depending on the mechanism of myocardial damage.<sup>[41]</sup>

Currently, there are only a few reports of ischemic myocardial injury in COVID-19 patients.<sup>[27]</sup> Recently, in a case series of 18 COVID-19 patients with ST-segment elevation, nine patients underwent coronary angiography, and coronary obstructive disease was found in six of them.<sup>[42]</sup> Therefore, it seems that MI with nonobstructive coronary is a more prevalent cause of ST-segment elevation when compared to the general population.<sup>[38]</sup>

Consideration of the acute coronary syndrome mechanism has a great impact on clinical management. Due to the pandemic, in some centers have encouraged the use of fibrinolysis before coronarography.<sup>[43]</sup> Considering the risks of fibrinolysis, this treatment modality should be only considered in patients, in whom the diagnosis of type 1 MI is certain. In fact, European Society of Cardiology (ESC) recommendations reinforce that primary percutaneous coronary intervention is the gold standard intervention, leaving fibrinolysis only when the primary approach is not feasible.<sup>[44]</sup>

## MYOCARDITIS AND STRESS CARDIOMYOPATHY

During acute viral infection, nonischemic myocardial injury may occur due to stress-cardiomyopathy or myocarditis, either due to direct cardiomyocyte damage or activation of the immune system. So far, only case reports of myocarditis have been published, and the actual prevalence remains unclear.<sup>[45-47]</sup> Interestingly, myocardial damage may not correlate with respiratory severity, as indicated by the case

of acute myopericarditis presenting with mild respiratory symptoms published by Inciardi *et al.*<sup>[46]</sup>

The distinction between stress-cardiomyopathy and myocarditis requires cardiac magnetic resonance imaging and endomyocardial biopsy (EMB), which may be limited in the setting of the ongoing pandemic. Magnetic resonance imaging provides a noninvasive morphological and functional evaluation that supports myocarditis suspicion; nevertheless and alike all imaging exams it should only be used when the results are expected to impact management and prognosis. Moreover, short protocols for image acquisition are recommended.<sup>[48]</sup>

EMB is the gold standard for establishing the diagnosis of myocarditis. However, in the setting of SARS-CoV2 infection, EMB should only be considered in life-threatening conditions after Acute coronary syndrome (ACS) and other causes of acute myocardial injury have been ruled out.<sup>[41]</sup> Two reports of EMB in COVID-19 patients were published, and one of them fulfilled criteria for myocarditis, with acute inflammatory T-lymphocyte infiltration, cardiomyocyte necrosis, and diffuse edema, but importantly without detection of SARS-CoV2 genome.<sup>[47]</sup> Indeed, so far, no viral particles have been detected in EMB in COVID-19 patients. Since myocardial injury develops late after the onset of symptoms (10–15 days), it has been proposed that immune-mediated lesion is the prevailing pathway in myocardial inflammation.<sup>[2]</sup>

The diagnosis of fulminant myocarditis has been suggested in some cases.<sup>[41,42,49,50]</sup> Tavazzi *et al.* reported a case of fulminant myocarditis with cardiogenic shock requiring mechanical circulatory support, although EMB only revealed mild inflammation, and the COVID-19 RNA was only detected in the inflammatory cells.<sup>[51]</sup>

There is no consensus regarding a specific treatment for SARS-CoV2 myocarditis. Of note, a case of fulminant myocarditis successfully treated with intravenous glucocorticoids, immunoglobulins, and mechanical support was recently reported.<sup>[52]</sup>

## HEART FAILURE AND CARDIOGENIC SHOCK

Zhou *et al.* reported heart failure in 23% of COVID-19 patients (52% in nonsurvivors vs. 12% in survivors), although echocardiography data were not reported.<sup>[2]</sup> In another study, among patients with a previously normal left ventricle ejection fraction admitted to ICU, one-third evolved with acute heart failure and cardiogenic shock.<sup>[15]</sup> Importantly, cardiogenic shock may dominate the clinical course. In a retrospective analysis of 68 COVID-19 diseased patients, 7% were due to myocardial damage with circulatory failure, and circulatory dysfunction was a contributing factor to mortality in one-third of the cases.<sup>[7]</sup>

A cohort with 100 patients was evaluated with serial echocardiography during COVID-19 progression. At baseline, the most common changes were RV dilation and reduced pulmonary acceleration time.<sup>[53]</sup> These findings are suggestive

of increased pulmonary artery resistance, which may occur due to pulmonary or vascular disease.<sup>[53]</sup> Of note, further progression of the RV parameters was observed in the patients who evolved with clinical deterioration.<sup>[53]</sup>

## CYTOKINE RELEASE SYNDROME

Similar to previous coronavirus infections, COVID-19 course may be complicated with cytokine release syndrome, a systemic pro-inflammatory state that may cause multisystem organ failure. This inflammatory state appears to be triggered by an imbalance between type 1 and type 2 T-helper cells response.<sup>[54]</sup> Several studies reported high pro-inflammatory cytokine levels in COVID-19 patients and described a direct correlation between cytokine serum concentration and disease severity.<sup>[2,54]</sup> Furthermore, interleukin-6 and ferritin levels were found increased in COVID-19 nonsurvivors.<sup>[2]</sup>

Recently, immune dysregulation, as measured by lymphocyte counts, C-protein reactive level, and procalcitonin concentration, was independently associated with myocardial injury.<sup>[55]</sup> From a cardiovascular standpoint, cytokine release syndrome-related cardiotoxicity may manifest with hypotension, dysrhythmias, left ventricular dysfunction, and cardiogenic shock.<sup>[56]</sup>

## CARDIAC ARRHYTHMIAS

During SARS-CoV and MERS outbreaks, a higher prevalence of both bradyarrhythmia and tachyarrhythmia events was detected; thus, it is likely that in the SARS-CoV2 pandemic the same phenomenon occurs.<sup>[57]</sup> Furthermore, cardiac arrhythmias may be the first presentation in COVID-19 patients, as found in a cohort of 137 patients, in which palpitations constituted the presenting symptom in 7.3% of patients.<sup>[58]</sup> The underlying pathophysiology is multifactorial and includes increased automaticity and enhanced triggered activity induced by hypoxemia, electrolyte derangements, and neuroinflammatory stress. In addition, heart failure decompensation and myocardial ischemia both predispose to arrhythmic events.

Wang *et al.* reported arrhythmic events in 16.7% of COVID-19 patients, with a significantly higher frequency in ICU patients (44.4% vs. 6.9%,  $P < 0.001$ ).<sup>[36]</sup> However, the type of arrhythmia was not discriminated in that study. Recently, in a study with 138 hospitalized patients, malignant arrhythmias with associated myocardial injury were detected in 5.9% of patients.<sup>[39]</sup>

Nevertheless, to the time being, a thorough description of the arrhythmia in the context of COVID-19 is yet to be published.

## THROMBOTIC DISEASE

Multiple mechanisms predispose to thrombotic events during systemic viral infections, with emphasis on the hypercoagulability induced by endothelial dysfunction, hypoxia, cytokine storm, and immobilization related to illness.

Similar to other infections, thrombotic complications are

more common in COVID-19 patients suffering from severe disease. Klok *et al.* reported thromboembolic events in 31% of patients with pulmonary embolism (PE), accounting for 85% of cases.<sup>[59]</sup> In a cohort of patients undergoing computed tomography pulmonary angiography, PE was detected in 24%, one-third of them presenting proximal PE.<sup>[60]</sup> Importantly, the rate of PE was even higher among ICU admitted patients, reaching 50%, and this impressive high prevalence was seen even though all patients were under prophylactic anticoagulation.<sup>[60]</sup> In addition, case reports of massive PE with acute RV dysfunction have also been published.<sup>[61,62]</sup>

Disseminated intravascular coagulopathy (DIC) is a marker of severe sepsis complicated with excessive thrombotic and bleeding events. DIC has been described in COVID-19 and associates with increased mortality (71.4% vs. 0.6%  $P < 0.001$ ).<sup>[63]</sup> In a cohort of 191 patients, D-dimer levels at admission  $>1 \mu\text{g/mL}$  were strongly associated with in-hospital mortality (adjusted hazard ratio: 18.4; 95% CI: 2.6–128.6;  $P = 0.003$ ).<sup>[2]</sup> Other coagulation disturbances, such as increased fibrin degradation product levels and prolonged prothrombin time, have been associated with mortality.<sup>[63]</sup> It has been suggested that DIC may cause myocardial injury. Supporting this theory, coronary artery thrombosis with myocardial necrosis was observed in autopsies of COVID-19 patients with DIC, and the elevation of D-dimer was detected in COVID-19 patients with MI.<sup>[42]</sup>

The high prevalence of thrombotic events in COVID-19 and the association with adverse outcomes may support the rationale of therapeutic anticoagulation in patients with elevated D-dimer, aiming to prevent microvascular thrombosis. Nevertheless, so far only one small study suggested the benefit of therapeutic anticoagulation in patients with high sepsis-induced coagulopathy score or markedly elevated D-dimer.<sup>[64]</sup>

Due to the lack of definitive data, scientific societies recommend advise on the use of empirical anticoagulation and give preference to the conventional prophylactic doses.

## CORONAVIRUS DISEASE 19 THERAPY

To date, no target therapy for COVID-19 has proven to be successful. Experimental and empirical treatments have been used worldwide, although their effectiveness remains controversial, and the side effects, particularly of cardiovascular nature, are considerable.

Chloroquine and hydroxychloroquine, a group of antimalarial drugs, were initially used extensively off-label due to promising *in vitro* results that were not confirmed on clinical trials, revealing no benefit in a randomized trial that included hospitalized patients.<sup>[65]</sup> These drugs are, on the other hand, associated with concerning side effects, like potential direct myocardial toxicity<sup>[66]</sup> and pro-arrhythmic effect due to potential prolongation and early afterdepolarizations, with the risk of initiating atrial and ventricular arrhythmias that may be

severe, sometimes even fatal.<sup>[57]</sup> The risk seems to be higher when used in combination with azithromycin since both drugs prolong the QT interval.<sup>[67]</sup>

The protease inhibitor lopinavir/ritonavir did not show any benefit when compared to placebo in severe patients.<sup>[68]</sup> In addition, it may prolong the QT interval, cause conduction disturbances<sup>[66]</sup> and induce multiple drug interaction by inhibiting CYP3A4 and P-glycoprotein, particularly with most P2Y<sub>12</sub> inhibitors and anticoagulant drugs.<sup>[69]</sup>

Regarding antivirals, remdesivir, an RNA-dependent RNA polymerase inhibitor, obtained the most favorable results. The preliminary results of a double-blind, placebo-control, randomized trial with 1063 hospitalized individuals revealed a significant reduction in time to recovery with a 10-day course treatment.<sup>[70]</sup> Importantly, the effect on survival is still unknown, as well as the impact on the cardiovascular system.<sup>[66]</sup>

Alternative classes of drugs besides antivirals are being evaluated for the management of COVID-19. Treatment with convalescent plasma is undergoing investigation with contrasting results so far. A multicenter study with 115 patients reported significant improvement defined by reduction in length of stay and necessity of invasive ventilation,<sup>[71]</sup> while a randomized trial with 103 patients detected no significant clinical improvement within 28 days, although there are concerns that the study may have been underpowered.<sup>[72]</sup>

On the rational of the increased cytokine release observed on severe patients, monoclonal antibodies targeting inflammatory mediators, such as interleukin-6 inhibitors (tocilizumab and sarilumab) are under investigation. The published preliminary results from randomized trials are controversial, as CORIMUNO-19<sup>[73]</sup> and COVACTA<sup>[74]</sup> report opposite outcomes regarding clinical improvement and risk of death; however, final results are pending. The impact on the cardiovascular system is still unclear.

Finally, the randomized control trial RECOVERY provided evidence that dexamethasone reduced 28-day all-cause mortality in patients requiring ventilation or oxygen support and with a disease course longer than 7 days. However, no benefit was observed in patients not requiring oxygen.<sup>[75]</sup> In addition, there are concerns of potential unreported side effects due to the short follow-up duration, particularly in patients with CVD.<sup>[76]</sup>

## LONG-TERM CONSEQUENCES

Evaluation of the long-term impact of COVID-19 on the cardiovascular system is still pending. On the follow-up of recovered patients from SARS-CoV infection, poor life-quality has been reported. When compared with healthy controls, patients presented a tendency to cardiovascular and glucose metabolism abnormalities, as well as other metabolic derangements such as an increase in serum phosphatidylinositol and lysophosphatidylinositol, known to play a role in glucose homeostasis.<sup>[77]</sup> Given the known similarities between the two

viruses, it will be relevant to evaluate the chronic CVD burden after SARS-CoV2 infection.

## CONCLUSIONS

Age and pre-existing CVD are the most important predictors of COVID-19 severity. The disease is associated with a high inflammatory burden and a propensity to cardiovascular complications. The most prevalent being acute myocardial injury, which was directly associated with disease severity and mortality. Multiple possible mechanisms may be accountable for this injury and when considering the ischemic injury, the nonobstructive coronary disease seems to be predominant. A better understanding of the virus pathophysiology, particularly the interaction with RAAS, may lead to new potential therapies.

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## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Coronavirus Disease (COVID-19) Pandemic. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. [Last accessed on 2020 Aug 31].
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20.
4. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;17:259-60.
5. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA - J Am Med Assoc* 2020;323:1239-42.
6. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846-8.
7. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020;94:91-5.
8. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-81.
9. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Wkly* 2020;8:113-22.
10. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, *et al.* Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020;109:531-8.
11. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA J Am Med Assoc* 2020;323:2052-9.
12. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, *et al.* Status of hypertension in China: Results from the China hypertension survey, 2012-2015. *Circulation* 2018;137:2344-56.
13. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of

- Covid-19. *N Engl J Med* 2020;382:2431-40.
14. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Itrrate E, Johnson SB, *et al.* Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020;382:2441-8.
  15. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients With COVID-19 in Washington state. *JAMA J Am Med Assoc* 2020;323:1613-4.
  16. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. *BMJ* 2020;369:m1966.
  17. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, *et al.* Obesity in patients younger than 60 years Is a risk factor for COVID-19 hospital admission. *Clin Infect Dis* 2020;71:896-7.
  18. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, *et al.* Obesity and mortality among patients diagnosed with COVID-19: Results from an integrated health care organization. *Ann Intern Med* 2020:M20-3742. doi: 10.7326/M20-3742. Online ahead of print.
  19. Jung CY, Park H, Kim DW, Lim H, Chang JH, Choi YJ, *et al.* *Clin Infect Dis* 2020 Aug 25;ciaa1257. doi: 10.1093/cid/ciaa1257. Online ahead of print.
  20. Vaduganathan M, Vardeny O, Michel T, McMurray JVV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;382:1653-9.
  21. Zhong J, Basu R, Guo D, Chow FL, Byrns S, Schuster M, *et al.* Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. *Circulation* 2010;122:717-28, 18 p following 728.
  22. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, *et al.* Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: Celebrating the 20<sup>th</sup> anniversary of the discovery of ACE2. *Circ Res* 2020;126:1456-74.
  23. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436:112-6.
  24. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, *et al.* Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;63:364-74.
  25. Chen D, Li X, Song Q, Hu C, Su F, Dai J, *et al.* Assessment of Hypokalemia and Clinical Characteristics in Patients With Coronavirus Disease 2019 in Wenzhou, China. *JAMA Netw Open* 2020;3:e2011122. doi: 10.1001/jamanetworkopen.2020.11122.
  26. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, *et al.* SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest* 2009;39:618-25.
  27. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417-8.
  28. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383:120-8.
  29. Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: From pathophysiology to practice. *J Am Coll Cardiol* 2009;54:2129-38.
  30. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute pneumonia and the cardiovascular system. *Lancet* 2013;381:496-505.
  31. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, *et al.* Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005;111:2605-10.
  32. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, *et al.* SARS-CoV2: Should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020;41:1801-3.
  33. Liu L, Qiu HB, Yang Y, Wang L, Ding HM, Li HP, Losartan, an antagonist of AT1 receptor for angiotensin II, attenuates lipopolysaccharide-induced acute lung injury in rat. *Arch Biochem Biophys* 2009;481:131-6.
  34. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875-9.
  35. Shenoy V, Kwon KC, Rathinasabapathy A, Lin S, Jin G, Song C, *et al.* Oral delivery of Angiotensin-converting enzyme 2 and Angiotensin-(1-7) bioencapsulated in plant cells attenuates pulmonary hypertension. *Hypertension* 2014;64:1248-59.
  36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA - J Am Med Assoc* 2020;323: 1061-9.
  37. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, *et al.* Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol* 2020;76:533-46.
  38. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.* Fourth universal definition of myocardial infarction 2018 European Heart Journal 2019;40:237-69.
  39. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811-8.
  40. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, *et al.* Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med* 2018;378:345-53.
  41. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;5:811-8.
  42. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, *et al.* ST-segment elevation in patients with Covid-19 - A case series. *N Engl J Med* 2020;382:2478-80.
  43. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: The protocols from Sichuan Provincial People's Hospital. *Intensive Care Med* 2020;46:1111-3.
  44. Chieffo A, Stefanini GG, Price S, Barbato E, Tarantini G, Karam N, *et al.* EAPCI position statement on invasive management of acute coronary syndromes during the COVID-19 pandemic. *Eur Heart J* 2020;41:1839-51.
  45. Doyen D, Mocerri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: A cause of raised troponin and ECG changes. *Lancet* 2020;395:1516.
  46. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, *et al.* Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:819-24.
  47. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, *et al.* Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur Heart J* 2020;41:1861-2.
  48. The European Society for Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. The European Society for Cardiology; 2020.
  49. Peretto G, Sala S, Caforio ALP. Acute myocardial injury, MINOCA, or myocarditis? Improving characterization of coronavirus-associated myocardial involvement. *Eur Heart J* 2020;41:2124-5.
  50. Chen C, Zhou Y, Wang DW. SARS-CoV-2: Apotential novel etiology of fulminant myocarditis. *Herz* 2020;45:230-2.
  51. Tavazzi G, Pellegrini C, Maurelli M, Belliati M, Scitti F, Bottazzi A, *et al.* Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *European Heart Journal* 2020;ehaa190. <https://doi.org/10.1093/eurheartj/ehaa190>.
  52. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *European Heart Journal* 2020;ehaa190:<https://doi.org/10.1093/eurheartj/ehaa190>.
  53. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, *et al.* Spectrum of cardiac manifestations in COVID-19: A systematic echocardiographic study. *Circulation* 2020;142:342-53.
  54. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
  55. Li D, Chen Y, Jia Y, Tong L, Tong J, Wang W, *et al.* SARS-CoV-2-induced immune dysregulation and myocardial injury risk in China: Insights from the ERS-COVID-19 study. *Circ Res* 2020;127:397-9.
  56. Jamal FA, Khaled SK. The cardiovascular complications of chimeric antigen receptor T cell therapy. *Curr Hematol Malig Rep* 2020;15:130-2.
  57. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and

- arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol* 2020;31:1003-8.
58. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, *et al.* Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)* 2020;133:1025-31.
  59. Klok FA, Kruip MJ, van der Meer NJ, Arbous MS, Gommers DA, Kant KM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145-7.
  60. Bompard F, Monnier H, Saab I, Tordjman M, Abdoul H, Fournier L, *et al.* Pulmonary embolism in patients with COVID-19 pneumonia. *Eur Respir J* 2020;56:2001365.
  61. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: A random association? *Eur Heart J* 2020;41:1858.
  62. Ullah W, Saeed R, Sarwar U, Patel R, Fischman DL. COVID-19 complicated by acute pulmonary embolism and right-sided heart failure. *JACC Case Rep* 2020;2:1379-82.
  63. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844-7.2.
  64. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020;18:1094-9.2.
  65. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, *et al.* Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med* 2020 Jul 23;NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Online ahead of print.
  66. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, *et al.* COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* 2020;116:1666-87.2.
  67. Chorin E, Wadhvani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, *et al.* QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. *Heart Rhythm* 2020;17:1425-33.
  68. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787-99.2.
  69. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, *et al.* Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol* 2020;75:2352-71.
  70. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al.* Remdesivir for the treatment of Covid-19 Preliminary report. *N Engl J Med* 2020;NEJMoa2007764. doi: 10.1056/NEJMoa2007764. Online ahead of print.
  71. Abolghasemi H, Eshghi P, Cheraghali AM, Imani Fooladi AA, Bolouki Moghaddam F, Imanizadeh S, *et al.* Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. *Transfus Apher Sci* 2020:102875. doi: 10.1016/j.transci.2020.102875. Online ahead of print.
  72. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, *et al.* Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and Life-threatening COVID-19: A randomized clinical trial. *JAMA* 2020;324:460-70.
  73. Pipeline Review. Tocilizumab Improves Significantly Clinical Outcomes of Patients with Moderate or Severe COVID-19 Pneumonia. Available from: <https://pipelinereview.com/index.php/2020042874458/Antibodies/Tocilizumab-improves-significantly-clinical-outcomes-of-patients-with-moderate-or-severe-COVID-19-pneumonia.html>. [Last accessed on 2020 Aug 31].
  74. Roche Provides an Update on the Phase III COVACTA Trial of Actemra/RoActemra in Hospitalised Patients with Severe COVID-19 Associated Pneumonia. <http://www.roche.com/investors/updates/inv-update-2020-07-29.htm>. [Last accessed on 2020 Aug 31].
  75. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with Covid-19 Preliminary report. *N Engl J Med* 2020;NEJMoa2021436. doi: 10.1056/NEJMoa2021436. Online ahead of print.
  76. Johnson RM, Vinetz JM. Dexamethasone in the management of covid -19. *BMJ* 2020;370:1-2.
  77. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, *et al.* Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Sci Rep* 2017;7:9110.