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Cardiovascular impact of COVID-19: an array of presentations

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Abstract. The novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) dominantly infects the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome (ARDS) however the cardiovascular implications of the infection are particularly significant, especially in their contribution to disease morbidity and mortality. SARS-CoV-2 enters the cardiovascular system by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. The pathogenic cardiovascular mechanism of the virus involves systemic inflammation via a cytokine storm and direct myocardial injury. The most frequently reported cardiovascular complications of COVID-19 include acute myocardial injury, myocarditis, myocardial infarction, heart failure, cardiomyopathy, arrhythmias, and venous thromboembolic events. Also, pre-existing cardiovascular disease in COVID-19 patients is a prime marker for attaining severe disease and is associated with high mortality rates. Lastly, the medications under investigation for COVID-19 may have their individual cardiovascular adverse effects. We hereby present a concise literature review that summarizes recent peer-reviewed and pre-print articles published on the cardiovascular implications of COVID-19. The information on the subject is being updated frequently therefore latest literature needs to be added in newly published reports for a better understanding of the topic. (www.actabiomedica.it)

Key words: cardiovascular; COVID-19; SARS-CoV-2; coronavirus; myocardial injury; myocarditis; cardiac

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease of viral etiology, caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). Owing to the swift spread of SARS-CoV-2 globally, COVID-19 was declared a pandemic on March 11, 2020 by the World Health Organization (WHO) (2). The first case of COVID-19 was reported on December 8, 2019 from Wuhan, situated in the Hubei province of China (3). Since then, the number of cases has risen exponentially in all parts of the world. China was the originating hub of COVID-19 however the epicenter shifted to Europe in February/March 2020 and then relocated to the USA in March/April 2020. As of June 13,2020, COVID-19 has affected 7 553 182 people and has resulted in 423 349 deaths worldwide, making it one of the biggest health threats of 21st century (4).

The typical progression of COVID-19 involves initial mild flulike illness transitioning to life-threatening acute respiratory distress syndrome (ARDS). Although pulmonary involvement remains the most dominant clinical manifestation of the disease, there is profound evidence of adverse disease outcomes linked to the cardiovascular complications induced by COVID-19. Also, pre-existing cardiovascular disease (CVD) is associated with increased susceptibility to COVID-19, severe disease form, and worse prognosis (5-7).

This review aims to highlight and enlist the various cardiovascular (CV) manifestations reported among COVID-19 patients. The contribution of pre-existing CVD in disease outcome is also discussed in the subsequent text. We have also provided a brief overview of the properties and pathophysiology of SARS-CoV-2, which enable it to hamper the CV system specifically. The CV adverse effects and probable drug interactions of potential COVID-19 therapies are reported.

The information on this subject is rapidly evolving, and not all dimensions of the clinical CV aspects of COVID-19 are known hence there is an urgent need for compact literature insights such as reviews that can equip practitioners with the latest, up-to-date research knowledge.

Methods

A thorough literature search on the cardiological implications of COVID-19 was carried out until 23rd June 2020, using PubMed, Google Scholar, and coronavirus related collection of all significant publishing databases. Search terms included "coronavirus", "SARS-CoV-2", and "COVID-19" in combination with "cardiovascular", "cardiac", "cardiac injury", "myocardial injury", "myocarditis", "myocardial infarction", "cardiomyopathy", "arrhythmia", "heart failure", "venous thromboembolism", "treatment", "therapy" and "pharmacology." This review aims to amplify the present understanding of the cardiovascular complications of COVID-19.

Properties and pathophysiology of SARS-CoV-2

SARS-CoV-2 is a member of the Coronaviridae family. The Coronaviridae family shares a set of common properties, and therefore SARS-CoV-2 is inherently a single-stranded, enveloped virus with a positive-sense ribonucleic acid (RNA) genome (8, 9). Coronaviruses are further categorized into four genera: alpha-, beta-, gamma- and deltacoronaviruses. Overall, seven coronaviruses can infect humans. Middle east respiratory syndrome (MERS) virus and severe acute respiratory syndrome (SARS) virus are two betacoronaviruses which can potentiate a severe respiratory illness. COVID-19 is the seventh identified human coronavirus. It has been termed as SARS-CoV-2 by the WHO (10). It is speculated that SARS-CoV-2 originates from bats as its nucleotide sequence is 86-96% identical to that of bat coronaviruses (11).

Studies suggest that SARS-CoV-2 initiates cell entry by binding to the human angiotensin-converting enzyme 2 (ACE2) receptor, a mechanism shared by the coronavirus family (12). ACE2 is a key membrane protein, responsible for multiple physiologic functions. It is highly expressed in the lung (primarily in Type II alveolar cells) and serves as a predominant entry site for the virus (10,13). When the virus binds to the ACE2 receptor, the lung-protective pathway is deregulated, thereby enhancing viral pathogenicity; this is how ACE2 plays an integral role in lung protection (14). ACE2 fragments into angiotensin II, a proinflammatory marker in the lung. ARDS and multiorgan dysfunction in COVID-19 are known to be precipitated by inhibition of ACE2, which leads to lung injury and systemic inflammation through a cytokine storm (10, 13, 14). Following the sequelae, cardiac demand is increased as systemic inflammation destabilizes atherosclerotic plaques in vessels, and the cytokine activity is already high due to the infection being viral, like in influenza (15, 16). ACE2 is also expressed in the heart where it combats high angiotensin II levels in conditions such as hypertension, atherosclerosis, and congestive heart failure (17). However, a recent study proposes that SARS-CoV-2 can cause direct cardiac tissue damage via utilizing ACE2 receptors; this is suggestive of a likely mechanism of COVID-19 linked CVD (18). Apart from direct myocardial injury and systemic inflammation, CVD in COVID-19 is also linked to electrolyte imbalance secondary to critical systemic illness. Hypokalemia, manifesting because of an abnormal renin-angiotensin-aldosterone cycle in COVID-19, is another topic of concern. Hypokalemic episodes can precipitate lethal tachyarrhythmias (19).

Role of pre-existing CVD in COVID-19 patients

Subjects with underlying CVD are supposedly more vulnerable to develop COVID-19, along with an increased propensity to severe disease and worse prognosis (1, 3, 5, 20). Most studies report the prevalence of pre-existing CVD in COVID-19 patients; Table 1 lists down a few of such studies along with their respective fatality outcomes. The link of pre-existing CVD to mortality is affirmed by the results of a study of 44,672 COVID-19 affected patients which revealed that a positive history of CVD increased the case fatality rate (CFR) by five-fold, in comparison to patients with no CVD (10.5% vs. 2.3%) (3). A meta-analysis involving 1527 COVID-19 patients from China reported that

Table 1. Cohorts highlighting cardiovascular manifestations in SARS-CoV-2. Abbreviations: ND, Not disclosed; DIC, disseminated intravascular coagulation; VT, Ventricular tachycardia; VF, Ventricular fibrillation; HF, heart failure; HR, heart rate; bpm, beats per minute; pt, patient

Authors	Number of patients	Cardiovascular disease, n (%)	Cardiovascular manifestations	Troponin	Mortality, n (%)
Huang et al (1)	41	6 (15%)	Shock (7%) Acute cardiac injury (12%)	Elevated in 12%	6 (15%)
Zhou et al (7)	191	15 (8%)	Acute cardiac injury (17%) HF (23%) HR >125bpm (1%) Hypotension (1%)	Elevated in 17%	54 (28.2%)
Wang et al (20)	138	20 (14.5%)	Shock (8.7%) Arrhythmia (16.7%) Acute cardiac injury (7.2%)	Mean 6.4pg/mL	6 (4.3%)
Shi et al (26)	416	44 (10.6%)	Chest pain (3.4%) Acute cardiac injury (19.7%) Abnormal ECG findings: ST-segment depression, T wave depression and inversion and Q waves (in 14/22 patients with cardiac injury)	Elevated in 19.7%	57 (13.7%)
Guo et al (27)	187	66 (35.3%)	VT/VF (5.9%)	Elevated in 27.8%	43 (23.0%)
Ruan et al (41)	150	ND	Myocardial damage/heart failure in 5 non-survivors (3.3% overall; 7% among non-survivors) Fulminant myocarditis suspected in few cases	ND	68 (45%)
Chen et al (47)	274	23 (8%)	HR >100bpm (38%) Acute cardiac injury (44%) HF (24%) Shock (17%) DIC (8%)	Median troponin concentration higher in deceased pts (40.8 pg/mL) than in recovered pts (3.3pg/mL)	113 (41.2%)
Arentz et al (50)	21	7 (33.3%)	Cardiomyopathy (33.3%)	Troponin level >0.3 ng/mL in 14%	11 (52.4%)

the prevalence of diabetes, CVD, and hypertension was 9.7%, 16.4%, and 17.1%, respectively (5). Moreover, the presence of CVD was associated with a 3-fold higher risk of contracting severe disease and intensive care unit (ICU) admission as compared to the 2-fold similar risk for both diabetes and hypertension. Quite strikingly, the frequency of CV comorbidities and its influence on the prognosis of COVID-19 seems to follow a geographical alignment. CFR was considerably higher in European countries and America than in China (4). Recent data from Italy further presents high mortality rates in patients with comorbidities (21). With evolving disease dynamics worldwide, it is important to stratify COVID-19 patient data according to the prior CVD presentation.

When possible CVD mechanisms in COVID-19 were assessed, higher age was regarded as a fundamental risk factor for enhancing both COVID-19 susceptibility and severity. Exemplary of this, the CFR was reported to be as high as 14.8% in COVID-19 patients

≥80 years (22,23). It is worth highlighting that CVD contributed much to mortality in this illness than the pre-existing chronic obstructive pulmonary disease (COPD), a revelation of prime importance (22). Also, unlike in other diseases, smoking and COPD history are far less significant parameters in determining disease severity in hospitalized COVID-19 patients than the history of CVD. Although conflicting data exists, it is postulated that increased ACE2 expression in patients with CVD enhances the vulnerability to acquire SARS-CoV-2 (6). Conclusively, additional studies in the field are required to determine the clear-cut connection of CVD and COVID-19 outcomes.

Cardiovascular manifestations of COVID-19

Figure 1 illustrates the most common CV complications associated with COVID-19. Likewise, *Table 1* summarizes the key cardiovascular presentations in population groups assessed in multiple COVID-19 studies; the incidence of pre-existing CVD and mortality are also reported.

Myocardial Injury and Myocardial Infarction: Direct myocardial injury in COVID-19 subjects can occur via myocardial ischemia or through nonischemic processes such as in myocarditis (7). COVID-19 studies have defined myocardial injury as the elevation of cardiac troponin I (TnI) or troponin T(TnT) to > 99th percentile of the upper reference limit or the presence of new electrocardiographic or echocardiographic abnormalities (1, 7). In a meta-analysis which analyzed 341 patients, the standardized mean difference (SMD) value suggested that patients with severe COVID-19-related illness had increased levels of TnI compared to those with less severity (SMD, 25.6ng/L; 95% confidence interval [CI]: 6.8 to 44.5ng/L) (24). Furthermore, Huang et al confirmed elevated high-sensitivity cardiac troponin I (hs -cTnI) levels (>28 pg/ml) in 5 out of 41 patients (1). ICU admission was required in 4 out of 5 patients with significantly higher levels of hs-cTnI, which is indicative of the severity of myocardial injury in COVID-19 patients. In retrospective cohort studies from China, the acute cardiac injury was reported in 7.2% to 17% of the hospitalized patients with COVID-19 illness and was more common among

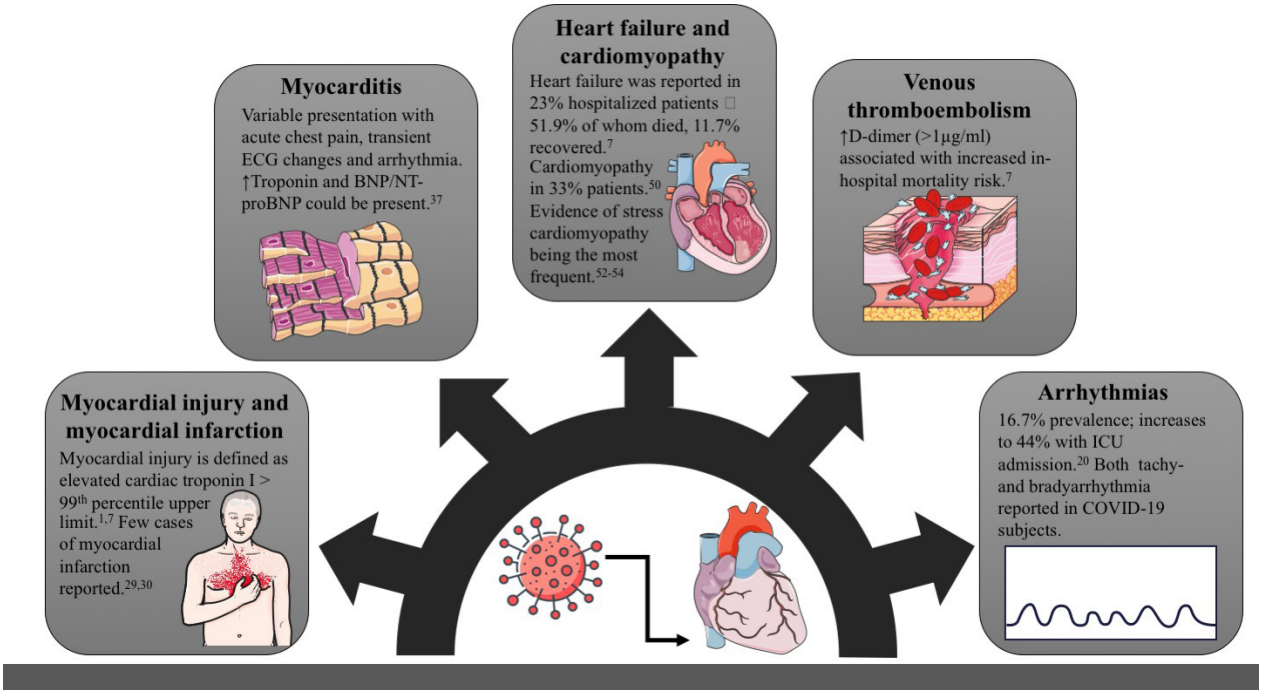

Figure 1. Cardiovascular manifestations of COVID-19.

ICU patients (22.2% vs. 2.0%; p < 0.001) and non-survivors (59% vs. 1%; p < 0.0001) (7, 10, 20). In a case-series of 419 confirmed COVID-19 patients, 383 patients were shifted to isolation wards, and 36 patients were admitted to ICU. ICU patients reportedly had significantly elevated hs-cTnI levels (25).

Shi et al emphasized the correlation between the myocardial injury in COVID-19 subjects to mortality (26). Out of 416 patients assessed in the study, there were 57 non-survivors. Among non-survivors, coronary artery disease (CAD) was reported in 10.6% of the patients, 5.3% had cerebrovascular disease, and 4.1% had heart failure. Approximately 82 patients (19.7%) had cardiac injury manifested by hs-TnI levels higher than the 99% percentile upper reference limit. The mortality rate was higher in patients with significant myocardial damage than those with none (51.2% vs. 4.5%) (26). Similar outcomes were reported in a study by Guo et al in which 52 of 187 hospitalized patients had cardiac injury signified by elevated TnT levels (27). The in-hospital mortality rate was also significantly increased in these patients. Also, the levels of TnT and N-terminal pro-B-type natriuretic peptide (NT-proBNP) surged during hospitalization in patients who died from COVID-19 (27).

Acute viral illnesses can result in profound systemic inflammatory sequelae and hemodynamic changes that may confer risk for rupture of atherosclerotic plaque and thrombus formation, resulting in either an ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (28). Kwong et al discussed the association between acute myocardial infarction (MI) and influenza and proposed that patients with severe respiratory infections are more susceptible to develop acute MI following influenza and non-influenza viral infections such as those acquired from coronavirus species (incidence ratio: 6.1 vs. 2.8) (15).

Unanimously, scarce data reports the Type 1 MI incidence in the context of COVID-19. Siddamreddy et al presented the case of a 61-year-old female with an acute inferior wall STEMI, who was later affirmatively diagnosed with COVID-19 (29). A drug-eluting stent was placed and aspiration thrombectomy was done. Following the stent placement, her electrocardiogram (EKG) was done again, which showed the resolution of ST-elevation changes. Bangalore et al also presented a case series of 18 COVID-19 patients with ST-segment elevation in their EKGs; 8 patients were clinically diagnosed with MI, out of which 6 patients had confirmed obstructive CAD on coronary angiography (30). In comparison, the remaining ten patients were diagnosed with noncoronary cardiac injury. Four of the patients clinically diagnosed with MI died in the hospital.

In a recent document, the American College of Cardiology discussed the non-specificity of abnormal troponin outcomes among patients with COVID-19. It postulated that abnormal troponin should not be solely regarded as proof of an acute MI, and other investigations should be prompted (31). Hence a designated diagnostic pathway should be outlined for COVID-19 patients with STEMI. For proper management of COVID-19 patients, published guidance statements should be considered (32).

Myocarditis: Viral pathogens commonly cause myocarditis, which is defined as marked inflammation of heart muscles. Previous studies regarding MERS and SARS demonstrate that coronavirus can lead to acute myocarditis (33, 34). So far, few cases of COVID-19 patients with a definitive diagnosis of myocarditis have been reported; some of them showed the presence of SARS-CoV-2 in myocardial biopsies while in others, only inflammatory infiltrates were found (35, 36). Myocarditis has a variable presentation as shown in *Figure 1*. Multiple imaging and investigational modalities can be used to confirm myocarditis. Echocardiography can be performed to demonstrate myocardial wall changes. A significant surge in cardiac biomarkers without obstructive CAD could manifest (37). Coronary computed tomography angiography should be the ideal approach to exclude concomitant CAD (38). However, for the confirmation of myocarditis, cardiovascular magnetic resonance (CMR) may be utilized if practical (39). Only clinically urgent CMR scans should be allowed (40). Although endomyocardial biopsy can be helpful in diagnosis, it is not a recommended diagnostic modality in COVID-19 patients with suspected myocarditis (37).

A retrospective study of 68 fatal cases and 82 recovered cases was presented by Ruan Q et al in which he investigated the cause of death among the

fatalities (41). 36 patients died of pulmonary failure, 5 patients died of myocardial damage, and 22 patients died of both while remaining five died of unknown causes. CVD was more prevalent in fatal cases than the survivors, and patients had elevated troponin, myoglobin, C-reactive protein, interleukin-6, and serum ferritin, suggesting that some patients died of myocarditis. Several published case reports validate the association of COVID-19 with myocarditis. Inciardi et al presented a case of a 53-year-old woman with no history of cardiac illness developed acute myopericarditis without signs and symptoms of interstitial pneumonia (42). Her TnT and NT-proBNP levels were elevated. Also, her EKG demonstrated diffuse ST elevation. Her treatment regimen included corticosteroids, antiviral drugs, dobutamine, chloroquine, and medical attention for heart failure.

Coronavirus fulminant myocarditis is another life-threatening entity which can present without the accompanying symptoms of pulmonary involvement; early diagnosis and treatment is the key in these cases. Zeng et al reported the first case of a 63-year-old man with no history of cardiac illness presenting with the evidence of fulminant myocarditis (43). Cardiac biomarkers showed an elevated TnI (>11 ng/mL) and NT-proBNP (22,600 pg/mL). Initially, echocardiography disclosed a left ventricular ejection fraction (LVEF) of 32%. His treatment regimen included intravenous immunoglobulin, antiviral therapy, interferon α-1b, methylprednisolone, piperacillin-tazobactam, continuous renal replacement therapy and to reduce cardiopulmonary burden he was placed on extracorporeal membrane oxygenation. The patient's LVEF gradually improved to 68%, but then the patient died due to secondary infection in a later stage.

Myocarditis has also been reported in the younger population (44-46).Kim et al presented a case of a 21-year-old female with COVID-19 related myocarditis (44). Her cardiac biomarkers were elevated, and echocardiography showed severe left ventricular systolic dysfunction. Myocarditis, combined with COVID-19, was confirmed by multimodality imaging. If in COVID-19 induced myocarditis, the patient survives, then the myocardial function can be recovered, and the prognosis is considered good.

Heart Failure and Cardiomyopathy: Acute heart failure is a less commonly reported presentation of COVID-19. It was reported in 23% of the hospitalized patients, with its prevalence being higher in non-survivors as compared to survivors (51.9% vs 11.7%, p<0.0001) (7). In a retrospective study of 799 hospitalized COVID-19 patients in Wuhan, heart failure was a positive finding in 24% of patients and was associated with high mortality risk (47). However, it is still vague as to whether heart failure in COVID-19 is a consequence of new cardiomyopathy or is an aggravation of former unidentified heart failure (48). Most recently, Belhadjer et al reported a case series of 35 pediatric patients with acute heart failure potentially associated with SARS-CoV-2 infection (31 patients tested positive) and the multisystem inflammatory syndrome in children, LVEF was <30% in the one-third population however it was restored in 25 out of 35 of those who were discharged from the ICU (49).

Cardiomyopathy may contribute to the development of heart failure syndrome. In a case series of 21 critical COVID-19 patients, cardiomyopathy was reported in 7 (50). Juusela et al confirmed that two of the seven pregnant COVID-19 patients developed cardiomyopathy (51). Takotsubo/stress cardiomyopathy is the reported cardiomyopathy in COVID-19 subjects (52-54). The immense emotional stress at the population level and respiratory inflammation caused by COVID-19 are considered the potential triggers for this pathology.

Venous thromboembolic event: Coagulation abnormalities are a peculiar finding in COVID-19 patients. COVID-19 prompts the likelihood of developing venous thromboembolism (VTE), especially in its course of hospitalization (55,56). Immobility during hospitalization and a fledging acute viral illness such as pneumonia are prime risk factors for initiating thrombotic events (57,58). Other factors that contribute to increased risk of VTE in COVID-19 infection are systemic inflammation, deranged coagulation profile, and multiorgan dysfunction (1,7,55,56,59). Several studies report elevated D-dimer levels as a fundamental finding in COVID-19 infected individuals, suggestive of severe coagulation pathway defects (1,7,59). Also, raised D-dimer levels are further connected to adverse outcomes and severity of the disease. As revealed in a cohort study done in China, elevated D-dimer levels (greater than 1g/L) were significantly proportional to the in-hospital mortality rate however this cutoff

was not diagnostically specific for VTE (7,20). High D-dimer levels and thrombocytopenia in COVID-19 are related to a higher risk of requiring mechanical ventilation and a low survival rate (60-62). Two subsets of VTE, namely disseminated intravascular coagulation (DIC) and pulmonary embolism, are not uncommon in the setting of SARS-CoV-2. These manifestations are further linked to the worst prognosis and enhanced mortality rates in the affected individuals. According to Tang et al, DIC was a key pathology in 71.4% of non-survivors (59). A study involving 25 COVID-19 patients revealed that elevated D-dimer was a consistent finding in all patients, with a median value of 6.06μg/ml (63). Furthermore, 10 out of these 25 patients had a median D-dimer level of 11.07μg/ml and were diagnosed with pulmonary embolism on computed tomography pulmonary angiography. A study by Tang et al proposed that anticoagulants such as low molecular weight heparin were more successful in dropping mortality ratios in severe COVID-19 infections as well as in patients having D-dimer higher than six times the standard upper cutoff, as compared to nonusers (64). However, the efficacy of heparin in mild COVID-19 cases still needs to be validated.

Recently, a published study provided concrete evidence of the development of deep venous thrombosis (DVT) in hospitalized COVID-19 patients (65). 46.1% of patients developed DVT, with distal DVT being twice as common as proximal DVT (65.2% VS 34.8%). Patients with DVT were older than patients without DVT. Also, the presence of DVT was linked to poorer disease prognosis, including a high mortality rate and reduced probability of being discharged. The incidence of DVT in COVID-19 is high and cannot be ignored. Thromboprophylaxis for high-risk patients (with Padua protection score ≥ 4) was commenced in this study, which led to promising disease outcomes.

Arrhythmias: According to recent literature insight, palpitations may be experienced by over 7% of COVID-19 patients (66). This percentage spiked to 44% in COVID-19 subjects who were admitted to ICU. A spectrum of arrhythmias has been reported in COVID-19 studies, however, no single arrhythmogenic mechanism has been attributed to this viral illness. In a study by Yu et al, sinus tachycardia was regarded as the most frequent manifestation among SARS affected individuals, with a significant prevalence of 72%; also, tachycardia persisted in 40% of patients even after one month of hospital discharge (67). Sinus bradycardia, on the other hand, was seen in 14.9% of patients and atrial fibrillation (AF) was reported in only 1 out of 121 individuals. Theoretically, sinus tachycardia in COVID-19 patients has been linked to multiple physiological causes of an infection such as fever, anxiety, inflammatory stress, and hypoxia (68). COVID-19 induced hypoxemia can potentiate life-threatening atrial fibrillation, especially in the elderly. In such a setting, AF can present even before the classic pulmonary manifestations of COVID-19, and the anticoagulant therapy is rendered complicated with an already evolving systemic inflammatory response (69,70). A recent analysis of 138 COVID-19 patients in China concluded that arrhythmias were the second most common complication in the subjects after ARDS, with an incidence of 16.7% (20) In an analysis of 187 SARS-CoV-2 positive patients by Guo et al, ventricular arrhythmias (both fibrillation and tachycardia) were found in 5.9% individuals (27). Alarmingly, this incidence surged to 11.5% in subjects with elevated troponin T levels. It is proposed that clinicians should always put acute coronary syndrome, acute myocarditis, and cardiac injury in their differential diagnosis in patients presenting concomitantly with arrhythmias and elevated serum troponin levels (68).

Therapeutic options for COVID-19 and their cardiovascular effects

At present, there are no approved therapies for COVID-19. Multiple drugs are being investigated, and while these therapeutic strategies are analyzed, their CV side effects are also monitored. Another important investigational aspect is testing the drug interactions of these suspected anti-COVID drugs, primarily with that of CV drugs. The potential therapies for COVID-19, their CV side effects, and interactions with CV drugs are discussed in Table 2.

Antiviral therapy: As of 2020, antivirals remain the most critically important medications understudy for COVID-19 treatment. Remdesivir, a nucleoside analog, initially developed for the Ebola outbreak, was also found to be effective against SARS/MERS invitro (71,72). Importantly, remdesivir and ribavirin are known to work by attaching to the

Table 2. Potential COVID-19 therapies: their cardiovascular adverse effects and drug interactions (68).

Abbreviations: AV, atrioventricular; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; VT, ventricular tachycardia; VF, ventricular fibrillation; IL, interleukin

	Drug name	Mechanism of Action	CV side effects	CV Drug Class Interactions
Antivirals	Remdesivir	Nucleotide-analog inhibitor of RNA dependent RNA polymerases	Unknown	Unknown
	Lopinavir/ritonavir	Lopinavir is a protease inhibitor Ritonavir inhibits CYP3A metabolism	Altered cardiac conduction: QTc prolongation, torsade de pointes, AV block	Antiplatelets Anticoagulants Statins Antiarrhythmics
	Ribavirin	Used in combination with Lopinavir to inhibit RNA and DNA virus replication	Can cause severe hemolytic anemia, avoid use in patients with significant / unstable cardiac disease	Anticoagulants
Antimalarials	Chloroquine/ hydroxychloroquine	Alters endosomal pH required for virus/cell fusion	May cause direct myocardial toxicity, exacerbate pre-existing cardiomyopathy, Altered cardiac conduction: AV block, Bundle Branch block, QT prolongation, torsade de pointes, VT/VF	Antiarrhythmics
Corticosteroids	Methylprednisolone	Alters gene expression to reduce inflammation	Hypertension Fluid retention Electrolyte disturbances	Warfarin
Biologics	Tocilizumab	Inhibits IL-6 receptor	Hypertension Increase serum cholesterol	Antiplatelets Anticoagulants Statins Beta blockers Antiarrhythmics

active site on RNA-dependent RNA polymerase on SARS-CoV-2 (73). On the other hand, drugs such as lopinavir/ritonavir inhibit the replication of RNA and have been used in combination with ribavirin against SARS associated coronavirus (74). Ribavirin and lopinavir/ritonavir are still being run in clinical trials to determine their efficacy against COVID-19. For years, these drugs have been used in the treatment of hepatitis C and HIV. Lopinavir/ritonavir have proven to be beneficial against MERS as they demonstrated decreased viral load in the condition (75).

Ribavirin is known for its cardiotoxicity in patients with chronic hepatitis C, the evidence of which was provided in a case report by Sakabe M et al (76). However, no direct CV effects of ribavirin could be associated with COVID-19. Lopinavir/ritonavir have reflected a narrow therapeutic window, which resulted in QT and PR interval prolongation in patients having baseline EKG abnormality (prolonged QT interval) or those taking QT-prolonging drugs (77). Additionally, lopinavir may have drug interactions with CYP3A4 mediated drugs like factor Xa inhibitor apixaban, therefore, dose reduction may be required (78).

HMG CoA reductase inhibitors like lovastatin and simvastatin specifically are contraindicated to be given alongside lopinavir as these can cause myopathy due to elevated statin levels (77).

Antimalarial therapy: Recently chloroquine and hydroxychloroquine have amassed quite an attention concerning COVID-19 treatment; both are antimalarial agents known to inhibit in-vitro activity in SARS-COV-2 by increasing lysosomal pH optimal for cell-virus fusion (79). Although chloroquine is well-known for its safety profile, it is associated with cardiotoxicity, when the safe dose is exceeded. Chloroquine-induced cardiac toxicity presents as heart failure and dilated cardiomyopathy, with the mechanism of action being intracellular inhibition of lysosomal enzymes (80) Furthermore, chloroquine can increase serum levels of beta-blockers (metoprolol, propranolol) via CYP2D6 inhibition; therefore, vigilant monitoring of heart rate and blood pressure is required. Lastly, studies have reported evidence of QT interval prolongation resulting from the concomitant use of hydroxychloroquine and azithromycin (81,82).

Other treatment options: Corticosteroids like methylprednisolone, are currently being investigated in retrospective studies of COVID-19 patients, especially in those who developed ARDS and have given favorable prospects by reducing the mortality rate (83). However, steroids precipitate fluid retention leading to hypertension as one of its cardinal CV side effects. Also, methylprednisolone interacts with warfarin, so this drug combination must be observed cautiously by clinicians.

Ibuprofen, a non-steroidal anti-inflammatory drug, is often used in the symptomatic management of viral illnesses, however recent evidence has raised questions as it can potentially trigger severe disease in COVID-19 patients, especially in those suffering from hypertension and diabetes mellitus via populating ACE2 receptor (a recognized site for viral entry in COVID-19 infection) (84). However, the data is limited, and WHO has not recommended its avoidance in COVID-19.

A recent case series showed that transfusion of convalescent plasma into critically ill COVID-19 patients improved clinical outcomes however, these results require further validation in prospective clinical trials (85). Likewise, patients with COVID-19 may benefit from interleukin-6 antibodies as the disease mechanism consists of a cytokine storm that needs to be tamed.

Interleukin-6 antibodies have been successful in mitigating the sequelae of inflammation in transplant patients, but still, very little clinical data support this hypothesis in the scenario of COVID-19 (86). Fortunately, there is no literature evidence of adverse cardiovascular effects associated with interleukin-6 antibodies (87).

ACE2 targeting drugs and their potential implications: ACE2 acts as a gateway receptor ensuring viral entry in the COVID-19 pathogenesis. Few studies hypothesize that ACE inhibitors (ACEI) and Angiotensin receptor blockers (ARBs) may increase the expression of ACE2, which in turn increases the patient susceptibility to the virus (6,88). In contrast, other studies suggest that ACEI/ARBs can accentuate the lung-protective function of ACE2 (1,89,90). Thus, there is inadequate data that deciphers probable associations of ACEI/ARBs therapy with acquiring COVID-19.

Conclusion

CV complications of COVID-19 are relatively new findings and therefore clinicians and nurses need to be acquainted with the latest literature and guidelines on the subject, to effectively treat COVID-19 patients.

List of Abbreviations: ARDS: Acute respiratory distress syndrome; ACEI: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers, ACE2 receptor: Angiotensin-converting enzyme 2 receptor; AF: Atrial fibrillation; CV: Cardiovascular; CVD: Cardiovascular disease; CMR: Cardiovascular magnetic resonance; CFR: Case fatality rate; COPD: Chronic obstructive pulmonary disease; CI: Confidence Interval; CAD: Coronary artery disease; COVID-19**:** Coronavirus disease; DVT: Deep venous thrombosis; DIC:Disseminated intravascular coagulation; EKG**:** Electrocardiogram; hs-cTnI**:** High-sensitivity cardiac troponin I; ICU**:** Intensive care unit; LVEF: Left ventricular ejection fraction; MERS: Middle east respiratory syndrome; MI**:** Myocardial infarction; NT-proBNP**:** N-terminal pro-B type natriuretic peptide; RNA**:** Ribonucleic acid; SARS:Severe acute respiratory syndrome; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2**;** SMD: Standardized mean difference; STEMI: ST-elevation myocardial infarction; TnI: Troponin I; TnT: Troponin T; VTE: Venous thromboembolism; WHO**:** World Health Organization

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