Impact of COVID-19 on the Cardiovascular System: A Review of Available Reports

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Abstract
The recent emergence of the coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China is now a global health emergency. The transmission of SARS-CoV-2 is mainly via human-to-human contact. This virus is expected to be of zoonotic origin and has a high genome identity to that of bat derived SARS-like coronavirus. Various stringent measures have been implemented to lower person-to-person transmission of COVID-19. Particular observations and attempts have been made to reduce transmission in vulnerable populations, including older adults, children, and healthcare providers. This novel CoV enters the cells through the angiotensin-converting enzyme 2 (ACE2) receptor. There is a higher risk of COVID-19 infection among those with preexisting cardiovascular diseases (CVD), and it has been connected with various direct and indirect complications, including myocarditis, acute myocardial injury, venous thromboembolism, and arrhythmias. This article summarizes the various cardiovascular complications and mechanisms responsible for the same with COVID-19 infection. For the benefit of the scientific community and public, the effect of COVID-19 on major vital organs such as the kidneys, liver, and intestines has been briefly discussed. In this review, we also discuss drugs in different stages of clinical trials and their associated complications, as well as the details of vaccines in various stages of development.

Keywords SARS-CoV-2 · COVID-19 · Cardiovascular diseases · Angiotensin-converting enzyme 2

Introduction
On March 11, 2020, the World Health Organization (WHO) declared the coronavirus disease a global pandemic. In December 2019, a group of pneumonia cases caused by a newly identified β-coronavirus was reported in Wuhan, China [1, 2]. On January 12, 2020, WHO named this coronavirus as the 2019-novel coronavirus (2019-nCoV). Then WHO officially called the disease coronavirus disease 2019 (COVID-19), and on February 11, 2020, the Coronavirus Study Group (CSG) of the International Committee proposed the name for the virus as SARS-CoV-2 [3]. On January 7, 2020, Chinese scientists isolated SARS-CoV-2 from a patient and determined the genome sequencing [4]. The virus has spread to over 20 countries, with 20,530,324 patients and 746,022 deaths as of August 12, 2020. The clinical observations of disease patterns reveal that infections have a direct impact on the cardiovascular system and, based on this revelation, the worldwide medical fraternities are demanding special care for patients with heart diseases. An earlier history of CVD influences the magnitude of COVID-19 infections, in most cases, and leads to clinical complications [5–7]. Case diaries of patients show that the viral infection causes injury to cardiomyocytes, and the reports from Li et al. (2020) point out that at least 8.0% of COVID-19 patients suffered acute myocardial injury [8] (Table 1).

In addition, individuals with preexisting cardiovascular risk factors such as hypertension and diabetes are exhibiting severe health consequences. One report from China reveals that out of 99 cases, cardiac-cerebrovascular diseases were reported for 40% of patients [9, 10]. In patients with cardiovascular and metabolic comorbidities, induced complications make
them prone to poor prognosis. Based on these findings, regulatory agencies and policymakers have alerted the public to the consequences of risks associated with these categories of people during infection. Thus, COVID-19 is now a matter of significant concern and attention to both biomedical and clinical research. The principal aim of this review is to reveal the link between CVD and COVID-19 infection and explain the science behind the same. We have also reviewed the impact of COVID-19 on other organs, therapies for control and management, and adverse cardiac effects associated with ongoing treatments.

**General Symptoms and Incubation Period of Virus**

Coronaviruses are enveloped positive-sense RNA viruses; under an electron microscope, they are revealed to have spike-like projections giving them a crown-like appearance; hence the name coronavirus [11]. The *Coronaviridae* family (order *Nidovirales*) has been classified into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Overall, evaluations indicate approximately 5% to 10% of acute respiratory infections are due to these viruses, and 2% of the population are healthy carriers of a CoV [12, 13]. Four coronaviruses can generally cause mild respiratory disease, i.e., HKU1, NL63, 229E, and OC43 have been in circulation among humans [14]. COVID-19 is caused by an RNA virus belonging to the genus Betacoronavirus [15]. The spike glycoprotein of the SARS-CoV-2 virus has two subunits: S1 and S2 (Fig. 1). S1 binds to the cell surface receptors, while S2 fuses with the cell membrane. TMPRSS2, a host transmembrane serine protease helps the virus access the cells by two diverse mechanisms; first, on the cell membrane surface, the spike S1 subunit binds to the ACE2, the ACE2 receptor is cleaved by the activation of the spike by TMPRSS2. Additionally, TMPRSS2 causes an irreversible conformational change by acting on the S2 subunit, leading to the virus fusion to the cell membranes; then it enters the cell [16–18].

Transmission occurs primarily via direct person-to-person contact or from an infected individual through droplets spread by coughing or sneezing. After viral exposure, the symptoms of COVID-19 become visible within 2–14 days, which includes fever, dry cough, and shortness of breath [19]. The severe cases showed respiratory, hepatic, gastrointestinal, and cardiovascular complications leading to mortality [20].

**COVID-19 and the Cardiovascular System**

Novel SARS-CoV-2 has been demonstrated to interact with ACE2, and enter the host’s cells, particularly cardiac...
myocytes and alveolar epithelial cells [21]. The ACE2 has a broad expression pattern in the human body with a powerful expression observed in the heart, lungs, gastrointestinal system, and kidneys. Additionally, ACE2 plays an essential role in the neurohumoral regulation of the cardiovascular system. The binding of SARS-CoV-2 to ACE2 causes acute myocardial and lung injury through the alternation in ACE2 signaling pathways [22]. ACE2 protects the heart against activation of the renin-angiotensin-aldosterone system (RAAS) because it converts angiotensin II to angiotensin (1–7). Angiotensin II is a vasoconstrictor, proinflammatory mediator, and damages capillary endothelium, while angiotensin (1–7) is a vasodilator. However, the virus entry causes down-regulation of ACE2 and increases angiotensin II levels, leading to increased heart damage. Thus, increased ACE2 receptor density will increase the viral load, but it remains likely to mitigate heart injury [23]. COVID-19 cases are escalating morbidity in patients with cardiovascular problems. Infection affects cardiac relevant biochemical pathways such as the ACE2 signaling pathway, cardiac muscle integrity, fibrinogen pathways, redox homeostasis, and induces a break in plaque associated with the stent, and finally, aggravates a myocardial injury and dysfunction [24].

Hyper Coagulation in COVID-19

COVID-19 patients with a history of diabetes, hypertension, and stroke on ventilators who underwent serological testing, showed the presence of antiphospholipid IgA antibodies and anti β2glycoprotein I IgA and IgG antibodies. These antiphospholipid antibodies abnormally target phospholipid proteins, rarely leading to thrombotic events [25]. Studies have found that some patients have unusual coagulation functions, and almost all critically ill have a coagulation disorder [26, 27]. It is known that acute inflammatory response caused by severe infection or sepsis can affect the coagulation and fibrinolytic system in multiple ways. Additionally, there is a specific correlation between ACE2 and coagulation [28].

COVID-19 infected patients can have a higher risk of venous thromboembolism (VTE) [29]. Increased D-dimer levels (>1 g/L) was often linked with in-hospital death, as reported by a multicenter retrospective cohort study from China [30]. Studies from China pointed out that elevated D-dimer (>0.5 mg/L) was found in 260 (46%) of 560 patients. In another study, approximately 183 patients with a mean D-dimer concentration of 2.12 mg/L (range 0.77–5.27) did not survive and survivors had a concentration of 0.61 mg/L (0.35–1.29) [31, 32]. A small prospective study from Italy showed higher baseline D-dimer levels in 16 patients with ARDS admitted to ICU [33]. Tang et al. (2020) reported an elevated level of D-dimer and fibrin degradation products (FDP) for non-survivors compared to survivors. During the disease condition, approximately 71.4% of non-survivors fit the clinical guidelines for disseminated intravascular coagulation (DIC) [32]. Severely ill patients with long-term immobilization are naturally at higher risk for VTE. In such patients, because of vascular inflammation, endothelial dysfunction and a hypercoagulable state were seen. In some studies, in patients with novel coronavirus pneumonia (NCP), the abnormalities in the coagulation system can be seen, mostly in a hypercoagulable state, which can quickly induce thrombus formation [9, 10]. There may be local embolism in the small vessels and microvessels of the relevant target organs. Some critically ill patients with high D-dimer are expected to have deep vein thrombosis and aortic embolism. This will cause the condition to worsen sharply. Therefore, the abnormal concentration and activity of ACE2 may affect the coagulation system in acutely ill hospitalized patients [28]. For these patients, direct oral anticoagulants and antiviral treatments, unfractionated heparin/low molecular weight heparins, or mechanical prevention, are advised.

Myocardial Infarction and COVID-19

In COVID-19 patients, cardiac damage occurs in many ways. Infection, inflammation, and fever make the blood more prone to clotting and interfere with the body’s ability to dissolve clots. In some patients, even if their arteries do not have fatty, calcified flow-limiting blockages, they may suffer heart damage that imitates heart attack injury, and the situation is known as myocardial infarction type 2 [34]. This can happen when the heart muscle is deprived of oxygen, and oxygen deprivation is one of the clinical symptoms of COVID-19 [35]. The metabolic demand of many organs, including the heart, is increased during fever and inflammation. If the lungs are
infected, the stress level is increased, and this will affect the gas exchange, which can further reduce oxygen supply to the heart muscle. Since this virus directly affects the heart, patients with COVID-19 show cardiac muscle inflammation, including among groups who were previously healthy with no cardiac problems. This nature of inflammation leads to cardiac muscle damage, variations in heart rhythm, and disturbs the optimal blood pumping. A case report from Italy points out that even in the absence of lung damage in healthy adults, COVID-19 could affect heart function even after the acute phase is resolved. There are reports that some patients develop life-threatening myocarditis with COVID infection via severe inflammation in the heart muscle [36]. This can happen even in patients with no preexisting risk factors (Fig. 2).

Elevated troponin is an important prognostic marker in COVID-19, even in those without CVD. The highest mortality is in those with CVD and raised troponins, followed by those with raised troponins, but no CVD. Those with CVD, but no raised troponins, have lower mortality. The lowest mortality is in those with neither CVD nor raised troponins. Serial measurements of troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP) show a rising trend in those who do not survive compared to those who survive. In the latter, the levels remain stationary [37]. Guo et al. (2020) and Shi et al. (2020) present a report on a cohort study of 416 hospitalized patients with COVID-19 who had evidence of myocardial injury manifested by elevation of high-sensitivity troponin I (TnI) levels [37, 38]. A significantly higher in-hospital mortality rate (42 of 82 [51.2%]) was seen in patients with increased TnI levels compared with those without increased TnI (15 of 335 [4.5%]).

Moreover, TnI elevation was associated with higher mortality rates for those with myocardial injury. Their data provide additional novel insights that TnT levels are significantly connected with levels of NT-proBNP and C-reactive protein (CRP), proposing a relation between myocardial stress and inflammation. A report of 150 patients from the fever clinic of Tongji Hospital, Wuhan, showed that the hypersensitive C-reactive protein (hs-CRP) and serum creatinine levels were higher [39]. Patients with myocardial injury also have confirmation of more severe systemic inflammation, including greater leukocyte counts and higher levels of CRP, procalcitonin, and high levels of other biomarkers of myocardial injury and stress, such as elevated creatine kinase, myoglobin, and NT-proBNP [34]. Dr. Bonow and coauthors (2020) noted that patients with chronic coronary artery disease have an increased risk of developing acute coronary syndrome during severe infection. This condition leads to a drastic increase in myocardial demand during infection or critical systemic inflammatory stress that could lead to atherosclerotic plaque instability, rupture, vascular and myocardial inflammation [40]. Systemic inflammation can also result in coronary plaque rupture in CVD patients and cause stent thrombosis [41].

**Cytokine Storm and Heart Damage**

Multiple studies reported that inflammatory markers are increased with COVID-19 infection, ranging from CRP, ferritin,
interleukin-6 (IL-6), interleukin-1β (IL-1β), interferon-γ (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) [42–44], leading to cytokine storms. Therefore, they can be used as prognostic markers to conclude the severity of COVID-19 infection. The cytokine storm is a complex network of severe molecular events, including a clinical phenotype of systemic inflammation, multiorgan failure, hyper-ferritinemia. It is generated by the activation of an innumerable amount of white blood cells, including B cells, T cells, NK cells, macrophages, dendritic cells, neutrophils, monocytes, and resident tissue cells, such as epithelial and endothelial cells, which release high amounts of proinflammatory cytokines [45]. Several immune pathways and proinflammatory cytokines have been induced by SARS-CoV-2 infection, especially CC chemokine ligand (CCL)2, (CXC chemokine) CXCL2, CCL8, CXCL1, IL33, CCL3L1 in BALF and CXCL10, tumor necrosis factor superfamily TNF Superfamily Member 10 (TNFSF10), tissue inhibitors of metalloproteinases (TIMP)1, C5, IL18, amphiregulin, neuregulin1, IL10 in PBMC, indicating sustained inflammation and cytokine storm in patients [46]. In a retrospective, multicenter study in Wuhan, China, 150 confirmed COVID-19 cases reported that the mortality was due to virally driven hyperinflammation, which included elevated ferritin and IL-6 [43].

Patients with CVD are at higher risk of cytokine storms. A cytokine storm begins with the activations of cytokine secreting cells with innate and adaptive immune mechanisms. Further, patients who have COVID-19 with myocardial injury have clinical proof of a higher rate of acute respiratory distress syndrome, and they more frequently require assisted ventilation than those without myocardial injury [40]. Myocardial injury may occur through diverse mechanisms, mainly mediated via ACE2 and other proposed mechanisms of cardiac participation comprising cytokine storm, arbitrate among subtypes of T helper cells [30], and severe pneumonia causes hypoxia. This leads to ischemic cardiac tissue, which increases intracellular calcium leading to the apoptosis of cardiac myocyte [47]. This causes a troponin leak and an elevated BNP level. There are reports that in rabbits, coronavirus infection has resulted in acute and even chronic heart failure [48], which could be related to the human strain of coronavirus [49].

**Endothelial Dysfunction in COVID-19**

Endothelial cell injury plays a vital role in the pathogenesis of multi-organ failure in COVID-19. The endothelium is one of the largest organs in the human body [50]. The endothelial cells express ACE2 receptors, and the viral entry causes major clinical conditions such as high blood pressure [51–53], kidney disease [54], cerebrovascular and neurologic disorders [55, 56]. The cardiovascular system is protected by the endothelial cells, and the proteins they release will influence everything from blood clotting to the immune response. Endothelial damage leads to excessive cardiovascular impairment and causes extempore heart attacks in COVID-19. Endothelial cell damage may cause blood vessel inflammation, leading to plaque rupture and heart attack [57, 58]. Due to the devastating immune-inflammatory response and the subsequent cytokine storm, the heart status becomes exacerbated via inflammation-induced heart failure. The factors promoting endothelial dysfunction are discrepancies between reactive oxygen species production and nitric oxide reduction, remodeling of the left ventricle, fibrosis by differentiation of fibroblasts into myofibroblasts following monocytes secretion of transforming growth factor-beta (TGFβ) [59, 60]. In COVID-19 patients with comorbidities, the dysfunctional endothelial response to the infection could also induce activation of the coagulation pathway(s) [61]. Criel et al. (2020) and Bompart et al. (2020) reported the possibility of deep vein thrombosis and acute pulmonary embolism in COVID-19 patients [62, 63]. These data substantiate and hold up a fundamental SARS-CoV-2-related endothelial dysfunction with an augmented risk of venous thromboembolic disease, systemic vasculitis, endothelial cell apoptosis, and inflammation in various organs [64–67].

**Hypertension and COVID-19**

It is unclear whether uncontrolled blood pressure is a risk factor for acquiring COVID-19, or whether controlled blood pressure among patients with hypertension is or is not less of a risk factor. The results of pooled analysis data reported by Lippy et al. (2020) pointed out that hypertension might be linked with up to 2.5-fold more significant risk of lethal COVID-19, particularly with older individuals. In COVID-19 illness, through ACE2 receptors, the virus enters the lung, and patients with hypertension have worse outcomes than those with any other underlying condition [68]. In COVID-19 patients, hypertension and other forms of CVD were found frequently, and ACE inhibitors and angiotensin receptor blockers (ARBs) were often used for the treatment, which results in an upregulation of ACE2. There are hypotheses that ACE2-stimulating drugs used to treat hypertension can increase the risk of developing lethal COVID-19. Fang et al. (2020) reported that patients treated with ACE2-elevating drugs for hypertension, diabetes, or cardiac diseases are at increased risk for COVID-19 infection and should, therefore, be monitored for ACE2-modulating medications, such as ACE inhibitors or ARBs [69].

Contrary to this hypothesis, data from various cardiological societies support the continued use of ACE inhibitors or ARBs in patients with hypertension hospitalized with COVID-19 [70]. This strategy has significantly better survival compared with similar hypertensive patients not on these drugs. This hypothesis was derived in observational,
propensity score-matched analyses of over 3430 patients hospitalized at various Chinese hospitals during December 2019–February 2020. There are other reports from other affected countries to support this claim, and based on these clinical observations, all clinicians are advised to continue ACE inhibitors and ARB blockers for patients who are already on these drugs for their blood pressure [70]. More research is essential to identify the possible mechanistic association between COVID-19 and CVD outcomes. Lippy and Plebani (2020) [71] pointed out that the meta-analysis study data showed increased blood levels of procalcitonin, a peptide hormone produced by the thyroid gland, lungs, and intestine, are associated with more severe forms of COVID-19. There are reports that low platelet counts are also associated with an increased risk of severe disease and mortality in COVID-19 patients [72].

COVID-19 and Other Organs

ACE2 is not only the access of COVID-19 in the lung but also probably involved in the development of lung injury. Zuo et al. (2020) showed that ACE2 protein is mainly expressed in 1.4% of type II alveolar epithelial cells [73]. Kuba et al. (2020) and Imai et al. (2020) showed that blocking the renin-angiotensin signal pathway can improve severe acute lung injury caused by SARS-CoV spike protein, suggesting that RAAS, composed of ACE, angiotensin II, and type 1a angiotensin II receptor (AT1a), promote the pathogenesis of the disease, induce pulmonary edema, and impair lung function [74, 75]. Hence, ACE2 plays a role in improving severe pulmonary edema and acute lung failure as the RAAS counter regulator.

Genetic analysis by Zhang et al. [76] showed high levels of ACE2 expression in esophageal stratified epithelial cells and ileocolic absorbable epithelial cells, suggesting a potential route of transmission via the gastrointestinal system. Besides fever and cough, the most common infection symptoms are nausea, vomiting, and diarrhea, which is more severe in patients infected with COVID-19 than SARS-CoV and MERS-CoV [9, 77]. COVID-19 entry may be associated with ACE2 abnormal expression and dysfunction in the gastrointestinal tract, leading to intestinal inflammation [28]. ACE2/Ang-(1–7) axis is known as the main peptide on counteracting Ang II effects and reducing inflammation. The intestine is one of the possible target organs for COVID-19 infection, but whether the digestive system is a transmission route requires much further study [78].

COVID-19 can enter renal tubular cells by binding to ACE2 and can lead to cytotoxicity and abnormal renal function. Bile ducts are found to have a high abundance of the neo coronavirus receptor ACE2, while hepatocytes expressed a very low amount [79]. These show that liver damage in COVID-19 may be caused by the virus directly binding to ACE2-positive bile duct cells and causing bile duct dysfunction or toxic side effects caused by therapeutic drugs [80]. Direct entry of the virus to liver cells is not reported anywhere. These results suggest the need for attention to patients’ liver reactions, especially those related to bile duct cell function, and thus the need for special care for patients with neo coronary pneumonia who have an abnormal liver function.

Factors Affecting COVID-19 Infection

Innate Immunity in COVID-19

Innate immunity may be the key to defeat SARS-CoV-2 infection. It serves as the first line of antiviral defense and could participate in a significant role in the progression of the cytokine storm [81]. During infection, the viral genome attachment to the receptors activates the innate immune response signaling pathway. The cells of innate immunity are sentinels to recognize the viral invasion by binding to the coronavirus’s RNA. This leads to type I interferon (IFN-I) expression and other proinflammatory cytokines that defend against viral infection at the access place [82]. In innate immunity, macrophages are very significant, which acquire heterogeneous subsets, including monocyte-derived macrophages and tissue-resident population with an array of distinguishing characteristics from (classically activated macrophage) M1 to (alternatively activated macrophage) M2-like phenotype [83]. Wang et al. (2020) reported that ACE2 receptors in alveolar macrophages lead to the activation and secretion of inflammatory cytokines and monocyte infiltration to lungs after virus binding [84]. In severe conditions, the activation and accumulation of monocytes and macrophages generate abandoned cytokine storms that lead to the modification of the M1 to M2 phenotype of alveolar macrophages. This results in inflammatory injuries and fibrosis of respiratory tracts [84, 85].

Smoking and its Relationship with COVID-19

Smoking increases the risk of severe symptoms developing during COVID-19 infection. Studies stipulate that, compared to nonsmokers, smoker patients may have significantly augmented unfavorable health outcomes regarding COVID-19, in addition to being admitted to intensive care with the need for mechanical ventilation and severe health issues [86, 87]. Smoking is now identified as a risk factor for several other respiratory infections, such as colds, influenza, pneumonia, and tuberculosis [88]. Among patients with severe respiratory diseases, smoking is also related to the progression of acute respiratory distress syndrome, which is a significant problem for extreme cases of COVID-19 [89–91]. Various retrospective multicenter cohort studies from China pointed out that
smoking causes undesirable effects during COVID-19. A study conducted by Guan et al. (2020) pointed out that among a patient population of 1099, 17% were current smokers and showed very severe symptoms, and over 5% were earlier smokers [31]. There are some studies that show the severe risk associated with smokers during COVID-19 infection compared to nonsmokers [31, 92, 93].

**Impact of Gender in COVID-19**

It is also observed that men are more prone to COVID-19 complications than women. There are some scientific explanations for this. Sama et al. (2020) reported that in two independent cohorts of patients with cardiac problems, the concentration of ACE2 in plasma is higher in men than in women, neither an ACE inhibitor nor an ARB was associated with higher ACE2 plasma concentrations [94]. The findings might explain the higher incidence and fatality rate of COVID-19 in men. The adverse effect of COVID-19 activity is due to the renin-angiotensin system’s over-activation, and there are reports that the virus can activate a disintegrin and metalloproteases-17 (ADAM-17), which is a crucial regulator of tissue and plasma ACE2 and can cleave tissue ACE2 and increases plasma ACE2, which is more harmful. The presence of an excessive amount of ACE2 in plasma induces cardiac toxicity via renin-angiotensin overactivity. This enzyme also causes a systemic inflammatory response and reduces the cardioprotective effect of ACE2 in tissue. The reduction of ACE2 in tissue amplifies cardiovascular complications significantly, and therefore the inhibition of ADAM-17 is useful to protect COVID-19 patient’s hearts if there is no off-target effect [95, 96]. There are reports that in non-small cell lung cancer cell lines, estradiol increases the expression levels and activity of ADAM-17 [97]. This finding would suggest higher shedding of ACE2 in women and could, at least partially, explain the reduced incidence of COVID-19 in women compared to men [98].

**Aging and COVID-19**

The susceptibility and severity of COVID-19 in older patients show that age is also a strong risk factor. Aging is associated with depletion of immune power and a weak cardiovascular function. There are reports that older persons with CVD and reduced ACE2 levels will be expected to be more susceptible to the exaggerated inflammation with further reduction in ACE2 expression in the context of COVID-19, exhibiting greater disease severity. Besides this, diabetes and hyperlipidemia, which are the traditional CVD risk factors, can alter the immune functions. This dysregulated immunologic status could raise the risk of CVD occurrence [99–102]. Thus, CVD may be an indicator of immunologic dysregulation or aging, and it can indirectly relate to the prognosis of COVID-19. Similarly, in patients with hypertension and CVD, elevated expression of ACE2 may increase the vulnerability of SARS-CoV-2 [103].

**Drug Therapy in COVID-19**

The best strategy for preventing COVID-19 is to take preventive measures. There are no precise therapies approved by WHO, Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA) for COVID-19 [104–106]. Vaccines and monoclonal antibodies against SARS-CoV-2 are in various stages of development [107]. Several other therapies under investigation are at different lab experiment stages, which include drugs targeting SARS-CoV-2 cell invasion and replication [108]. An in vitro study indicated the efficacy of chloroquine (anti-malarial drug) and hydroxychloroquine (a medicine for rheumatoid arthritis or systemic lupus erythematosus treatment) in blocking SARS-CoV-2 cell entry is probably through affecting endosomal pH and by the glycosylation of ACE2 receptors [109]. The doses of the drugs used in the in vitro study were chloroquine 500 mg twice daily and hydroxychloroquine 400–600 mg twice a day, and trials with these agents are ongoing for patients [110–113]. Gautret et al. (2020) reported that in most COVID-19 patients, hydroxychloroquine is useful for clearing the viral nasopharyngeal carriage of SARS-CoV-2 within 3 to 6 days [114]. Pfizer has reported data on clinical trials performed in France against COVID-19. They used azithromycin (Zithromax) along with hydroxychloroquine [115]. Geleris et al. (2020) showed that hydroxychloroquine treatment was not associated with the risk of intubation or death. The results of the study should not be taken to preclude either benefit or harm of hydroxychloroquine treatment. In their study, the results do not support hydroxychloroquine at present, without outside randomized clinical trials testing its efficacy [116]. However, there are warnings from other groups on the effectiveness of these combinations in the majority of patients and regarding adverse cardiac effects [117, 118]. Azithromycin, a macrolide antibiotic drug, may prevent bacterial superinfection and have immunomodulatory properties to work as adjunct therapy [114, 119–122]. The HIV protease inhibitor lopinavir/ritonavir (Kaletra, AbbVie) is also not recommended because of negative clinical trial data and unfavorable pharmacodynamics.

Camostat mesylate (a serine protease inhibitor) approved in Japan for chronic pancreatitis and postoperative reflux esophagitis, among other indications, has been reported to block TMPRSS2 activity and thereby to inhibit SARS-CoV entry into cells [123]. This well-permitted therapy has been proposed as a treatment to prevent SARS-CoV-2 spike protein activation, thus preventing cell entry and controlling the
infection. Another drug recommended for treatment is remdesivir. This is a broad-spectrum antiviral that interrupts RNA replication by acting as a nucleotide analog [124] because it is primarily developed to treat Ebola and shown to have in vitro activity against SARS-CoV-2. It prevents the replication ability of MERS-CoV in human epithelial cells and mediates entry via human CoV receptors [109, 125]. It is safe in initial trials and is currently undergoing clinical trials in China, Europe, Japan, and the United States [126]. Previous studies report that their use has a clinical advantage in COVID-19 patients with a decrease in the severity of pneumonia and earlier clearance of virus [127]. However, as per regulatory agencies, data is insufficient to suggest for or against the new broad-spectrum antiviral remdesivir.

The antiviral medication oseltamivir, used for the treatment of influenza, has been tried by many patients in China for COVID-19 treatment [77]. Several of the current clinical trials used oseltamivir in the comparison group but not as a proposed therapeutic intervention [128], and this agent has no role in the management of COVID-19 once influenza has been excluded. Umifenovir (arbidol), an antiviral drug mainly for the treatment and prophylaxis of influenza, based on in vitro data suggesting activity against SARS, is currently approved in Russia and China for treatment against COVID-19 [129]. A minimal clinical experience has been described in China with umifenovir for COVID-19 treatment [130]. It is not established, but ongoing randomized clinical trials in China are testing the efficacy of umifenovir for COVID-19.

The combination of HIV protease inhibitor lopinavir/ritonavir was demonstrated to have in vitro activity against SARS-CoV. The drug acts by suppressing coronavirus activity by inhibiting the virus replication, and improved clinical outcomes were reported when used in combination with ribavirin for SARS [131]. There have been reports of its success in treating SARS-CoV-2, though the first randomized control trial did not demonstrate statistically significant benefit among hospitalized patients with COVID-19 [132]. Other proposed strategies include interferon and convalescent serum. IL-6 receptor antagonists used in the treatment of rheumatoid arthritis sarilumab and tocilizumab were also used against COVID-19. For treating acute cytokine release syndrome in patients, chimeric antigen receptor-T cell therapy is used [133]. These may be the possible therapies for COVID-19 patients with markedly elevated IL-6, ferritin, D-dimer, and hs-cTnI level, and those that display elements of cytokine storm or secondary hemophagocytic lymphohistiocytosis. Tocilizumab has been used with reported success for patients with severe COVID-19. There are reports that patients with COVID-19 have elevated levels of acute-phase reactants and inflammatory cytokines leading to cytokine release syndrome (CRS), and tocilizumab is effectively used in in-hospital patients admitted with CRS [134]. Kewan et al. (2020), in their retrospective cohort study, analyzed the resulted favorable outcomes in hypoxic COVID-19 patients who were consecutively admitted between March 13, 2020, and April 19, 2020, and treated with a single intravenous infusion of low-dose tocilizumab. By May, an increasing number of studies had reported the use of tocilizumab in treating COVID-19. A multicenter cohort study by Guaraldi et al. (2020) reported the role of tocilizumab in plummeting the risk of invasive mechanical ventilation/death in a cohort of patients with severe COVID-19 pneumonia with a standard of care treatment. They showed that both intravenous and subcutaneous tocilizumab administration might be capable of reducing the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia and can be confirmed with randomized clinical trials [135, 136]. Clinical trials with sarilumab just launched in the US [137–140] and are awaiting results. Monteil et al. [141] showed that clinical-grade human recombinant soluble ACE2 (hrsACE2), which has already been tested in phase 1 and 2 clinical trials [142, 143], can reduce the growth of virus in Vero E6 cells. Additionally, at the early stage of infection, they reported that hrsACE2 could significantly inhibit the infected human blood vessel organoids and kidney organoids. Clinical data are insufficient for the treatment of COVID-19 to suggest either for or against the use of convalescent plasma or hyperimmune immunoglobulin [144]. There are different opinions among various regulatory agencies to recommend immunomodulators such as interferons because of their toxicity and lack of sufficient data on the effectiveness in treating severe acute respiratory distress syndrome and MERS. Similarly, Janus kinase inhibitors, such as baricitinib, are not recommended because of their broad immunosuppressive effects [145].

There are some new data to correlate mortality rate and vitamin deficiency in COVID-19 patients. Medical researchers from Wuhan have recently registered (Identifier: NCT04264533) for a new clinical trial using vitamin C infusion for the treatment of SARS-CoV-2 infected pneumonia cases. In this investigation, intravenous vitamin C or a placebo control at a dose of 24 g/day for 7 days will be tested in 140 patients and will monitor the various needs for mechanical ventilation, organ failure scores and vasopressor drugs, ICU length of stay, and 28-day mortality [146]. Data analysis from ten countries revealed the relation between low vitamin D levels and hyperimmune active systems. Vitamin D strengthens innate immunity and prevents overactive immune responses. This finding could clarify why children are unlikely to die from COVID-19, and an aging population is severely affected by COVID-19. Based on these data, the medical fraternity made suggestions for using vitamin D supplementation to protect against SARS-CoV2 infection [147].
In their guidelines, panel members from the National Institutes for Health, Bethesda, suggested against the regular use of systemic corticosteroids for ventilated COVID-19 patients without ARDS. However, low-dose therapy for adult patients who are undergoing refractory shock is recommended [148]. Consumption of corticosteroids or nonsteroidal anti-inflammatory drugs for other conditions by COVID-19 patients should not be discontinued. Corticosteroids such as dexamethasone (NCT04327401) have broad effects on innate and adaptive immunity [149]. A trial published by the University of Oxford states that this drug cuts deaths in ventilated patients by one third and deaths in other admitted patients receiving oxygen by only one fifth [150, 151]. Although NIH guidelines recommended against the use of angiotensin-converting enzyme inhibitors or ARB for COVID-19 patients, these drugs should not be ceased for CVD patients who are already taking them. Similarly, statins can also be continued for patients with preexisting conditions and not be prescribed for COVID-19 outside of clinical trials. A very recent report suggests that nitric oxide is also being explored for therapeutic use in COVID-19 patients, utilizing its antiviral, antibacterial, and bronchodilation properties [152].

Recently, Cavalli et al. (2020) reported in their retrospective cohort study of patients with COVID-19 and ARDS that a high dose of anakinra, a recombinant interleukin receptor antagonist, was safe with clinical improvement in 72% of patients. This study is registered with ClinicalTrials.gov, NCT04318366, as a part of the COVID-19 Biobank study [153]. Pilkington et al. (2020) reported the effect of colchicine on clinical outcomes in ventilated patients with COVID-19. In a randomized multicenter clinical trial, colchicine’s potential was compared with the optimal medical treatment plus colchicine with optimal medical therapy alone (control group) among 105 patients from 16 Greek medical centers. This study concluded with a novel finding that the mechanism of colchicine’s action to treat COVID-19 may be antithrombotic and anti-inflammatory [158].

**Drug-Induced Cardiovascular Complications**

For the prophylaxis for COVID-19 infection, hydroxychloroquine and azithromycin have been used. Among all, the extensively used antibiotic, azithromycin, is most identified as a rare cause of QT prolongation [159, 160], serious arrhythmias [161, 162], and increased risk for sudden death [163]; higher age and female sex have been indicated as risk factors. This antibiotic can also cause non-pause-dependent polymorphic ventricular tachycardia. Electrophysiologic studies show that both drugs can cause proarrhythmia via mechanisms beyond the blocking of IKr implicated in usual cases of torsade de pointes [164, 165]. On the other hand, safety deliberations for using hydroxychloroquine and azithromycin in medical use have been described by a few authors [166]. For the treatment of COVID-19, there is not enough clinical information to suggest for or against the use of chloroquine or hydroxychloroquine. If used, however, clinicians should monitor patients for adverse effects, especially prolonged QT intervals.

**Vaccines at Various Stages of Development**

The human clinical testing for the first COVID-19 vaccine launched with unusual rapidity was on March 16, 2020. Approximately, 115 vaccine candidates, of which 78 are confirmed as active, and 37 are unconfirmed (development status cannot be determined from publicly available or proprietary information sources) as of April 8, 2020. Among the 78 confirmed active projects, 73 are currently in preclinical stages [167]. The vaccines recently under clinical trials include mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, INO-4800 from Inovio, LV-SMENP-DC and pathogen-specific aAPC from Shenzhen Gene-Immune Medical Institute, Covax-19™ from GeneCure Biotechnologies, ChAdOx1 nCoV-19 and MenACWY from the University of Oxford, Covaxin from Bharat Biotech, and ZyCOV from Zydus Cadila Healthcare [168–176].
Table 2  Vaccines under clinical trial for COVID-19

| Vaccine & developer | Status |
|---------------------|--------|
| mRNA-1273 Moderna   | Phase I |
| Ad5-nCoV Can Sino Biologicals | Phase I |
| INO-4800 Inovio     | Phase I |
| LV-SMENP-DC Shenzhen Geno-Immune Medical Institute | Phase I |
| aAPC Shenzhen Geno-Immune Medical Institute | Phase I |
| Covax-19™ Gene Cure Biotechnologies | Phase I |
| ChAdOx1 nCoV-19 University of Oxford | Phase I |
| MenACWY University of Oxford | Phase I |
| COVAXIN Bharath Biotech | Phase I |
| ZyCoV-D Zydas Cadila Health Care | Phase I |
| ZyCoV-E AstraZeneca | Phase II |
| ZyCoV-S Zydus Cadila Health Care | Phase II |

A summary of details of stages of various vaccines is given in Table 2.

Conclusion

COVID-19 is a global pandemic and is a significant health threat worldwide. There is an increase in morbidity and mortality in patients suffering from both cardiovascular complications and COVID-19. Therefore, more considerable attention is needed for viral infection related heart damage at the time of treatment. The cardiologist community has to play an essential role in managing and treating patients affected by this disease. Notably, better awareness of the link between the ACE2 protein, hypertension, and COVID-19 will be valuable for patients with both COVID-19 and CVD. The possibility of testing troponin levels in suspected communities as a primary screening protocol should be considered owing to the low cost and short time consumption. Some promising treatments are under investigation; however, none with proven clinical efficacy has been reported to date.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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