Circulation

IN DEPTH

COVID-19 and Cardiovascular Disease

ABSTRACT: Coronavirus disease 2019 (COVID-19) is a global pandemic affecting 185 countries and >3 000 000 patients worldwide as of April 28, 2020. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2, which invades cells through the angiotensin-converting enzyme 2 receptor. Among patients with COVID-19, there is a high prevalence of cardiovascular disease, and >7% of patients experience myocardial injury from the infection (22% of critically ill patients). Although angiotensin-converting enzyme 2 serves as the portal for infection, the role of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers requires further investigation. COVID-19 poses a challenge for heart transplantation, affecting donor selection, immunosuppression, and posttransplant management. There are a number of promising therapies under active investigation to treat and prevent COVID-19.

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Coronavirus disease 2019 (COVID-19) is a global pandemic. As of April 28, 2020, infected patients were present in 185 countries and there were >3 000 000 cases reported worldwide, with more than 210 000 fatalities.[1] The outbreak began in China, but the number of cases outside of China exceeded those in China by March 15, 2020, and rose at an exponential rate. The number of fatalities in several countries now exceeds the total in China. COVID-19 interacts with the cardiovascular system on multiple levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction.

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel single-stranded enveloped RNA virus is the 7th known human coronavirus. SARS-CoV-2 is unlike the coronaviruses known to cause the common cold (229E, OC43, NL63, and HKU1), but similar to the zoonotic severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) from 2002[2] and the Middle East respiratory syndrome (MERS) coronavirus from 2012.[3] SARS-CoV-2 is believed to have originated in bats, similar to many other coronaviruses, because it shares 89% to 96% nucleotide identity with bat coronaviruses.[4] Similar to SARS and MERS, it is believed that SARS-CoV-2 moved from bats to an intermediate host (possibly a Malayan pangolin, which shares 91% nucleotide identity) and then to humans[5] (Figure 1).

SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor after activation of the spike protein by transmembrane protease serine 2.[6] ACE2 is expressed in

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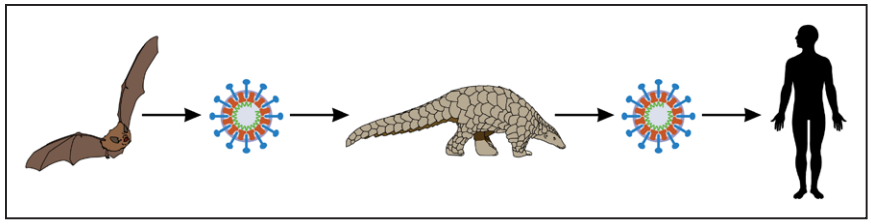

Figure 1. Suspected transmission pathway of severe acute respiratory syndrome coronavirus 2 to humans.

the lung (principally type II alveolar cells[7]) and appears to be the predominant portal of entry. ACE2 is highly expressed in the heart as well, counteracting the effects of angiotensin II in states with excessive activation of the renin-angiotensin system, such as hypertension, congestive heart failure, and atherosclerosis.[8] In addition to the heart and lung, ACE2 is expressed in the intestinal epithelium, vascular endothelium, and kidneys, providing a mechanism for the multiorgan dysfunction that can be seen with SARS-CoV-2 infection.[8,9] There is increasing evidence linking COVID-19 with increased morbidity and mortality from cardiovascular disease (CVD). In this review, we summarize the rapidly evolving data in this field.

CLINICAL PRESENTATION

SARS-CoV-2 is spread predominantly by respiratory droplets, but also can be aerosolized and has been detected in the stool. Transmission may occur from symptomatic or asymptomatic patients, with secondary infection rates ranging from 0.5% to 5%.[10,11] SARS-CoV-2 has been demonstrated to remain stable for up to 3 hours in the aerosolized form, up to 24 hours on cardboard, and as long as 3 days on plastic or stainless steel.[12] The median incubation time is 4 to 5 days and 97.5% of patients will experience symptoms within 11.5 days of exposure.[13,14]

Early reports suggest the most common symptoms are fever (88%) and dry cough (67.7%), which are shared with many other viral syndromes (Figure 2). Conspicuously, rhinorrhea (4.8%) and gastrointestinal symptoms (diarrhea 4% to 14%, nausea or emesis 5%) appear to be infrequent in COVID-19.[11] Reports from China demonstrate that a significant majority of patients (81%) had mild symptoms (no pneumonia or mild pneumonia) from COVID-19. Among patients with more substantial symptoms, 14% experienced severe symptoms (dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, or lung infiltrates >50% within 24 to 48 hours) and 5% were critically ill (respiratory failure, septic shock, or multiple organ dysfunction or failure).[9]

The case-fatality rate (CFR; number of deaths/number of diagnosed cases) has differed significantly around the world. The original reports from China suggested a CFR of 2.3%,[15] with subsequent reports estimating a lower symptomatic case-fatality risk (the probability of dying after developing symptoms) at 1.4%,[16] which contrasts with influenza (0.1%), MERS (34%), and SARS (10%).[17] Based on reported data from April 28, 2020, the CFR varies significantly by country: China, 5.5% (83 938 cases); Italy, 13.5% (199 414 cases); Iran, 6.3% (92 584 cases); Spain, 10.3% (232 128 cases); South Korea, 2.3% (10 752 cases); Germany, 3.9% (158 768 cases); and the United States, 5.6% (988 490 cases).[1] The CFR rises rapidly with increasing age; the CFR is <1% for patients <50 years of age, rising to 1.3% for 50-year-old patients, to 3.6% for 60-year-old patients, to 8% for septuagenarians, and to 14.8% for octogenarians.[15] The CFR increases with disease severity. There were no deaths reported among mild or severe cases in the Chinese cohort; however, the CFR was 49% among patients with critical illness. Furthermore, compared with patients with no comorbidities, in whom the CFR is 0.9%, patients with

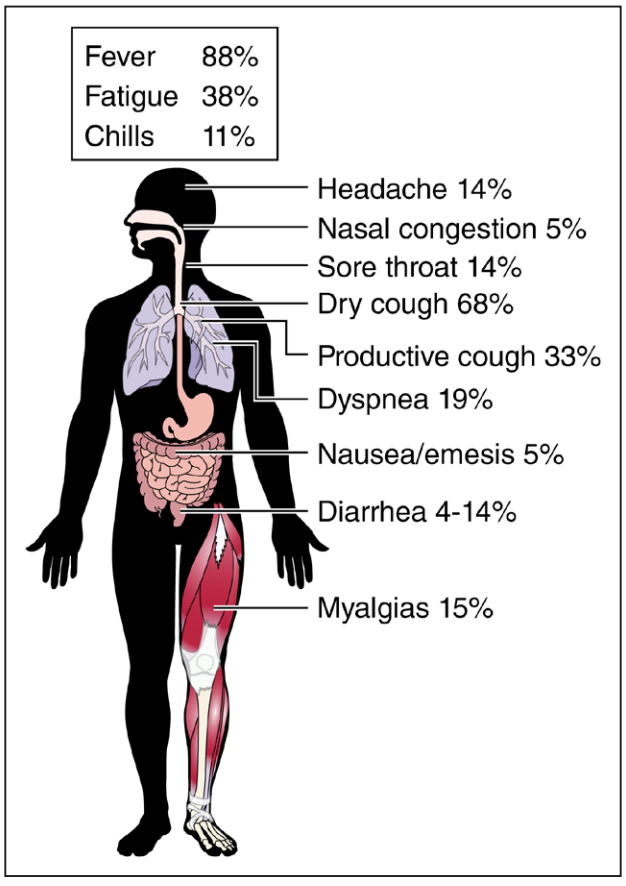

Figure 2. Symptoms of coronavirus disease 2019 (COVID-19).

medical comorbidities have a significantly increased CFR: 10.5% for CVD, 7.3% for diabetes mellitus (DM), 6.3% for chronic obstructive pulmonary disease, 6% for hypertension, and 5.6% for cancer.[15]

COVID-19 IN PATIENTS WITH CVD

CVD was a common comorbidity in patients with COVID-19 predecessors SARS and MERS. In SARS, the prevalence of DM and CVD was 11% and 8%, respectively, and the presence of either comorbidity increased the risk of death 12-fold.[2,18] DM and hypertension were prevalent in ≈50% of cases of MERS; CVD was present in ≈30% of patients.[19] The increased presence of cardiovascular comorbidities holds true for COVID-19 as well, most notably among those with more severe disease. In 1 cohort of 191 patients from Wuhan, China, any comorbidity was present in 48% (67% of nonsurvivors), hypertension in 30% (48% of nonsurvivors), DM in 19% (31% of nonsurvivors), and CVD in 8% (13% of nonsurvivors).[20] In a cohort of 138 hospitalized patients with COVID-19, comorbidities were similarly prevalent (46% overall and 72% in patients requiring intensive care unit [ICU] care), as were cardiovascular comorbidities: hypertension in 31% (58% in patients requiring ICU care), CVD in 15% (25% in patients requiring ICU care), and DM in 10% (22% in patients requiring ICU care).[21] Analysis of an outpatient and inpatient cohort of 1099 patients with COVID-19 revealed that 24% had any comorbidity (58% among those with intubation or death), with 15% having hypertension (36% among those with intubation or death), 7.4% DM (27% among those with intubation or death), and 2.5% coronary heart disease (9% among those with intubation or death).[13] Data from the National Health Commission of China demonstrated that 35% of patients diagnosed with COVID-19 had hypertension and 17% had coronary heart disease.[22] A recent metaanalysis of 8 studies from China including 46 248 infected patients showed the most prevalent comorbidities were hypertension (17%±7% [95% CI, 14% to 22%]) and DM (8%±6% [95% CI, 6% to 11%]), followed by CVD (5%±4% [95% CI, 4% to 7%]).[23] The mechanism of these associations remains unclear. Potential explanations include CVD being more prevalent in patients with advancing age, a functionally impaired immune system, or elevated levels of ACE2, or patients with CVD having a predisposition to COVID-19.

COVID-19 AND MYOCARDIAL INJURY

Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases in China. In the aforementioned study of 138 hospitalized patients with COVID-19 in Wuhan, China, cardiac injury (elevated high-sensitivity cardiac troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities) was present in 7.2% of patients overall and 22% of patients who required ICU care.[21] The report from the National Health Commission of China reported that almost 12% of patients without known CVD had elevated troponin levels or cardiac arrest during hospitalization.[22] Notably, hs-cTnI was >99th percentile upper reference limit in 46% of nonsurvivors as opposed to 1% of survivors[20] (Figure 3).

Early reports indicate that there are 2 patterns of myocardial injury with COVID-19. One study demonstrated that at 4 days after symptom onset, median hs-cTnI levels were 8.8 pg/mL in nonsurvivors versus 2.5 pg/mL in survivors. During follow-up, the median hs-cTnI among survivors did not change significantly (2.5 to 4.4 pg/mL), whereas it rose to 24.7 pg/mL on day 7, to 55.7 pg/mL on day 13, to 134.5 pg/mL on day 19, and to 290.6 pg/mL on day 22 in nonsurvivors.[20] Notably, the median time to death from the onset of symptoms was 18.5 days (interquartile range, 15 to 20 days). The rise in hs-cTnI tracks with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6, lactate dehydrogenase), raising the possibility that this reflects cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury. In contrast, reports of patients presenting with predominantly cardiac symptoms suggest a different pattern, potentially viral myocarditis or stress cardiomyopathy. For example, 1 case recently published described a man presenting with chest pain and ST-segment elevation on his ECG, but without coronary obstruction. An echocardiogram noted left ventricular dysfunction (ejection fraction 27%, left ventricular end diastolic diameter 5.8 cm) and elevated cardiac biomarkers (troponin T >10 ng/mL, NT-proBNP [N-terminal pro-BNP] >21 000 pg/mL).[24] After a therapeutic approach that included intravenous immunoglobulin and steroids, ejection fraction and cardiac biomarkers normalized within 3 weeks. In another report from China, a 63-year-old man with no cardiac history presented with both severe respiratory manifestation and evidence of fulminant myocarditis with an enlarged left ventricle (left ventricular end diastolic diameter 6.1 cm) and depressed left ventricular function (ejection fraction 32%). The patient had an elevated troponin I (>11 ng/mL) and NT-proBNP (>22 000 pg/mL). Given the severity of his cardiogenic shock, he was placed on extracorporeal membrane oxygenation and was treated with intravenous immunoglobulin, steroids, antiviral therapy, and renal replacement therapy. The patient ultimately showed recovery of his ventricular function within 2 weeks.[25] Both of these patients were treated with glucocorticoids but the impact of this therapy is unclear. The World Health Organization and Centers for Disease Control and Prevention do not recommend glucocorticoid use unless indicated otherwise

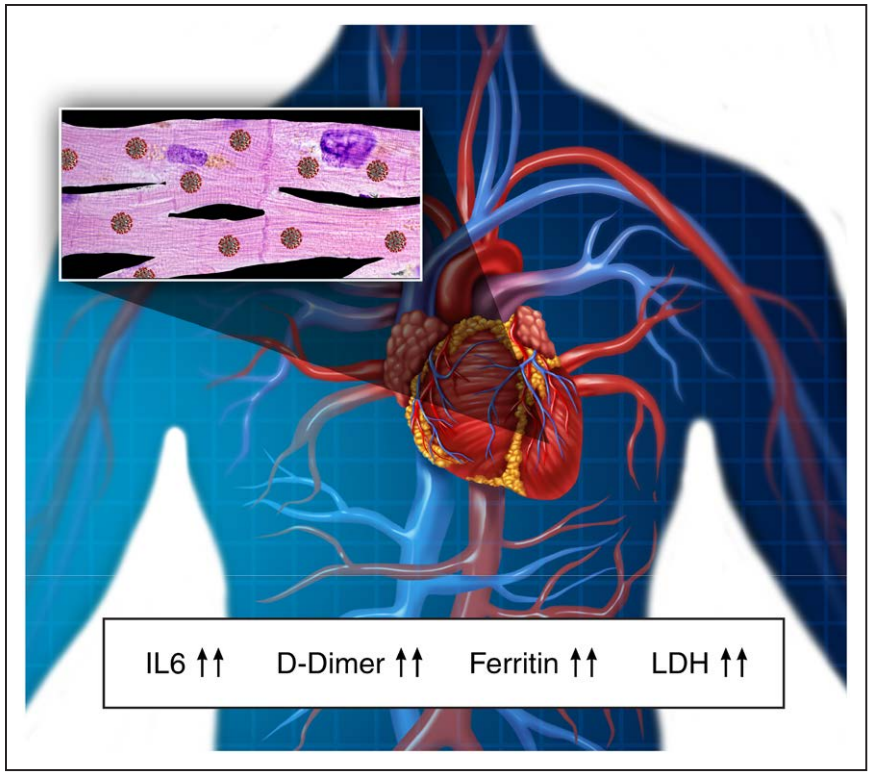

Figure 3. Myocardial injury from coronavirus disease 2019 (COVID-19) can be explained by 2 mechanisms.
Myocardial injury can result from the associated cytokine storm manifested by elevated levels of interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), and D-dimer or myocardial dysfunction from the direct effect of severe acute respiratory syndrome coronavirus 2 on the heart.

(eg, chronic obstructive pulmonary disease or asthma exacerbation).[26,27] Similarly, a report from the National Health Commission of China comments that a subset of patients presented with palpitations and chest pain, not the typical fever and cough.[22] Based on available but limited data, it appears that the incidence of fulminant myocarditis and profound cardiogenic shock is low; however, the rate of recovery and mode of treatment are yet to be determined.

The exact mechanism of cardiac involvement in COVID-19 remains under investigation. One potential mechanism is direct myocardial involvement mediated by ACE2. A murine model demonstrated pulmonary infection with SARS-CoV also precipitated an ACE2-dependent myocardial infection.[28] Among humans, during the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of autopsied hearts.[29] Other suggested mechanisms of COVID-19–related cardiac involvement include a cytokine storm, mediated by an imbalanced response among subtypes of T helper cells,[20] and hypoxia-induced excessive intracellular calcium leading to cardiac myocyte apoptosis.[22]

Role of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE2 is a homolog of angiotensin-converting enzyme that converts angiotensin II to angiotensin 1 to 7, thereby diminishing vasoconstriction mediated by the renin angiotensin system. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is common in cardiovascular disorders (hypertension, coronary artery disease, congestive heart failure, and DM). There are conflicting data on whether these drugs increase[30–32] or have minimal effect on ACE2 levels.[33–36] SARS-CoV-2 entry into cells is ACE2 dependent (Figure 4); however, ACE2 appears to be protective against acute lung injury. In a murine model, binding of the SARS-CoV spike protein to ACE2 caused ACE2 downregulation, leading to an increase in angiotensin II and ultimately increased pulmonary vascular permeability, inducing pulmonary edema and reduced lung function. Treatment with recombinant ACE2[37] and losartan[38] mitigated the degree of lung injury. Losartan is being studied for potential mitigation of lung injury among inpatients and outpatients with COVID-19.[39,40] At this time, nearly all major societies have recommended against adding or stopping angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or other renin-angiotensin-aldosterone system antagonists in this setting, unless done on clinical grounds independently of COVID-19, given the lack of evidence available on their potential benefit or harm.

Heart Transplantation in the Era of COVID-19

During previous coronavirus epidemics (SARS and MERS), transplant recipients presented with similar symptoms as the general population.[41,42] During the COVID-19 pandemic, a case study described the clinical courses of 2 heart transplant recipients from the Hubei province of China. Both patients presented with

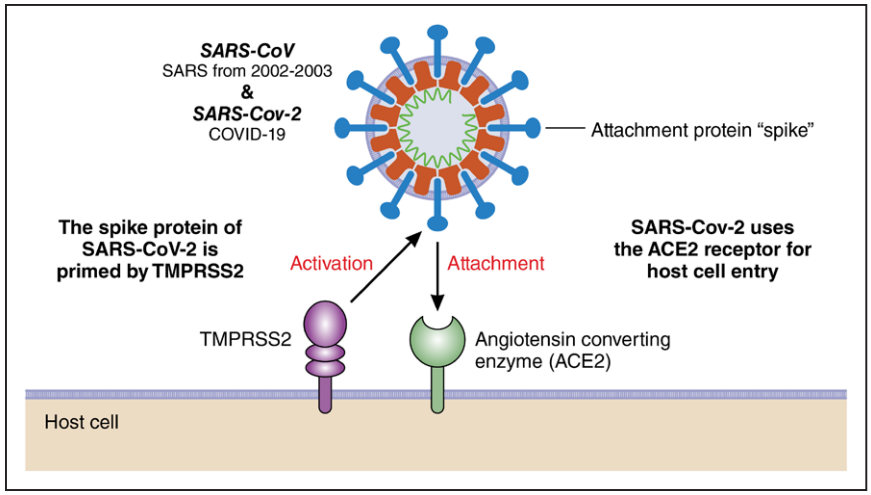

Figure 4. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 (ACE2) receptor after activation of the spike protein by transmembrane protease serine 2 (TMPRSS2).
COVID-19 indicates coronavirus disease 2019; SARS, severe acute respiratory syndrome; and SARS-CoV, severe acute respiratory syndrome coronavirus.

fever and had laboratory and computed tomography scan results that were similar to those of nonimmunosuppressed individuals, showing bilateral ground-glass opacities in a peripheral distribution. One had relatively mild disease and the other needed hospitalization and supplemental oxygen.[43] Both survived and were treated with antibiotic and antiviral agents. The patient who was hospitalized required cessation of immunosuppression, along with treatment with methylprednisolone and intravenous immunoglobulin. A survey of 87 heart transplant recipients in Wuhan, China, did not find a higher risk of infection with SARS-CoV-2 if routine preventive measures were used.[44] This finding needs to be confirmed in larger populations. Whether transplant recipients will experience differences in disease severity or duration compared with the nonimmunosuppressed population is unknown.

The ongoing pandemic has raised the question of whether to continue offering heart transplantation because of concerns about a risk for exposure to COVID-19 during hospitalization, as well as challenges in controlling the infection in the context of high levels of immunosuppression. Current recommendations are to continue heart transplantation without changes in immunosuppression provided the recipient has not tested positive for SARS-CoV-2 and has not had exposure to or symptoms of COVID-19 in the previous 2 to 4 weeks.[45,46] Major societal recommendations include avoiding donors with known or suspected COVID-19 and if a donor had COVID-19, he or she should be COVID-19 free (by polymerase chain reaction) for at least 14 days (owing to the incubation period of ≈5 days and onset of symptoms in ≈11.5 days).[14,47] We recognize the difficulty in making this decision with increasing prevalence of COVID-19 in the donor population, who may be asymptomatic, especially if the donor cannot be tested for COVID-19. The recommended management of transplant recipients who develop mild COVID-19, based on very limited data to date, is supportive care and continuation of immunosuppression with reduction of the antimetabolite (mycophenolate or azathioprine) and further treatment based on disease severity and drug availability.[45] Protease inhibitors are a potential treatment option for COVID-19, which will increase calcineurin inhibitor levels.

Treatment

Preventive measures are the best strategy in COVID-19. Vaccines and monoclonal antibodies against SARS-CoV-2 are in development, but a number of other investigational therapies, using repurposed clinically approved drugs targeting SARS-CoV-2 cell invasion and replication, may be considered. Recombinant human ACE2 (APN01) was developed in 2010 and could potentially both neutralize the virus and protect against acute lung injury. It has been demonstrated to be safe and reduce levels of both angiotensin II and interleukin-6 in a phase II study of acute respiratory distress syndrome.[48] It is under investigation in China in severe COVID-19. The serine protease inhibitor camostat mesylate, which is approved in Japan for chronic pancreatitis and postoperative reflux esophagitis, among other indications, has been shown to block transmembrane protease serine 2 activity and inhibit SARS-CoV entry into cells.[49] This well-tolerated therapy has been proposed as a treatment to prevent SARS-CoV-2 spike protein activation, thereby preventing cell entry and controlling infection. Remdesivir is a broad-spectrum antiviral agent that interrupts RNA replication by acting as a nucleotide analog.[50] Initially developed to treat Ebola virus disease, it has been demonstrated to have in vitro activity against SARS-CoV-2 and to prevent and reduce disease severity in MERS coronavirus in primates.[51,52] Remdesivir has been proven safe in previous trials and clinical trials are enrolling patients in China[53,54] and the United States.[55,56] Chloroquine (an antimalarial drug) and hydroxychloroquine (a rheumatoid arthritis and systemic lupus erythematosus treatment) block SARS-CoV-2 cell entry in vitro at similar concentrations that are achieved with treatment for rheumatoid

arthritis (500 mg twice daily for chloroquine and 600 mg twice a day loading followed by 400 to 600 mg/d for hydroxychloroquine) and trials with these agents are ongoing.[52,57–60] Early studies suggest clinical benefit in COVID-19 with reduction in pneumonia severity, decreased length of hospitalization, and earlier viral clearance.[61] The combination protease inhibitor lopinavir/ritonavir used to treat HIV infection was demonstrated to have in vitro activity against SARS-CoV and improved clinical outcomes when used in combination with ribavirin for SARS.[62] There have been reports of its success in treating SARS-CoV-2, although the first randomized, controlled trial did not demonstrate statistically significant benefit among hospitalized patients with COVID-19.[63] In this study of 199 patients, 28-day mortality was 5.8% lower (95% CI, 17.3% to 5.7%) for the lopinavir/ritonavir-treated patients and the median time to improvement was 1 day shorter. Further data are needed to determine the role of lopinavir/ritonavir in COVID-19 treatment. Antiviral medications typically used for influenza (oseltamivir and arbidol) have been applied, without clinical efficacy data available. Favipiravir, another drug approved for influenza treatment, is considered promising because it inhibits RNA polymerase, and is being studied in a clinical trial in China.[64] Other proposed strategies include interferon and convalescent serum use.

Tocilizumab and sarilumab are interleukin-6 receptor antagonists used in the treatment of rheumatoid arthritis, and tocilizumab also has indication for the treatment of cytokine release syndrome as is seen with chimeric antigen receptor T-cell therapy. These may be potential therapies for patients with COVID-19 who display elements of cytokine storm or secondary hemophagocytic lymphohistiocytosis with markedly elevated interleukin-6, ferritin, D-dimer, and hs-cTnI levels. Tocilizumab has been used with reported success in patients with severe COVID-19 and clinical trials are ongoing.[65–67] A trial of sarilumab just launched in the United States.[68]

CONCLUSIONS

COVID-19, caused by SARS-CoV-2, is a global pandemic evolving in real time. Cardiovascular comorbidities are common in patients with COVID-19 and these patients are at higher risk of morbidity and mortality. It is not known if the presence of cardiovascular comorbid conditions pose independent risk or whether this is mediated by other factors (eg, age). Myocardial injury is present in >25% of critical cases and presents in 2 patterns: acute myocardial injury and dysfunction on presentation and myocardial injury that develops as illness severity intensifies. Continuation of clinically indicated angiotensin-converting enzyme inhibitor and angiotensin receptor blocker medications is recommended based on the available evidence at this time. A number of promising treatments are under investigation, but none with proven clinical efficacy to date.

ARTICLE INFORMATION

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Disclosures

None.

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