Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Impact of COVID-19 infection on the cardiovascular system: An evidence-based analysis of risk factors and outcomes

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19, emerged in late 2019 in Wuhan, China. The World Health Organization declared the virus a pandemic on March 11, 2020. Disease progression from COVID-19 infection has shown significant symptom manifestations within organ systems beyond the respiratory system. The literature has shown increasing evidence of cardiovascular involvement during disease course and an associated increase in mortality among infected patients. Although the understanding of this novel virus is continually evolving, it is currently proposed that the mechanism by which the SARS-CoV-2 virus contributes to cardiovascular manifestations involves the ACE2 transmembrane protein. The protein ACE2 is highly expressed in blood vessel pericytes, and infection can result in microvascular dysfunction and subsequent acute coronary syndromes. Complications involving the cardiovascular system include myocardial infarction, arrhythmias, shock, and heart failure. In this evidence-based review, we discuss risk factors of cardiovascular involvement in COVID-19 infection, pathophysiology of COVID-19-related cardiovascular infection, and injury, COVID-19 effects on the cardiovascular system and corresponding treatments, and hematologic effects of COVID-19 and COVID-19 in heart transplant patients. Clinicians managing COVID-19 patients should appreciate the potential cardiovascular effects related to the disease process.

Introduction

Late 2019 marked the discovery and subsequent spread of unknown infectious pneumonia from Wuhan, China. This agent would be identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19 [1], with a basic reproduction rate of 2–2.5 (e.g., reproduction rate is an indication of virus transmissibility, reflecting average new infections generated by an infectious person in a naïve population; greater than 1, the number of infected would likely increase, and less than 1, transmission would likely die out) and a reported mortality rate between 0.1% and 9%. SARS-CoV-2 has rapidly spread across hundreds of countries leading the World Health Organization to declare the virus a pandemic on March 11, 2020 [1–3]. Globally, implementing public health policies to contain the virus was not uniform, leading to varying degrees of spread from country to country [4]. As of December 21, 2020, there have been at least 77,290,000 cases and at least 1,700,900 deaths worldwide [5].

It is important to note that the global impact of COVID-19 extends beyond the healthcare field; pandemic-related economic shutdowns have disrupted sectors including hospitality, tourism, restaurant, and entertainment [6]. In the US alone, trillions of dollars have been released to support the economy, but disruptions to the supply and demand of various industries will likely put pressure on GDP [6]. At an individual level, the psychological impact of the virus and forced quarantine can produce panic, anxiety, paranoia, and hoarding. Healthcare workers who are overworked and on the front lines are especially at high risk for post-traumatic stress disorder and burnout and depression [7]. Through evidence-based scientific research, a stronger understanding of the disease can reduce its negative impacts [8].

Much has already been discovered about the virus. SARS-CoV-2 is a single-stranded positive-sense RNA virus that is part of the Coronaviridae family of viruses. More specifically, COVID-19 is considered a

betacoronavirus – the other subsets being alphacoronavirus, gammacoronavirus, and deltacoronavirus [3]. The novelty of the virus has been attributed to the mechanism by which it infects a host. It has been previously shown that infection requires cleavage of viral S protein by endogenous TMPRSS2 and the presence of host ACE2 transmembrane proteins. It has been hypothesized that SARS-CoV-2 also contains gain-of-function mutations within receptor-binding domains and a mutation leading to a furin-protease cleavage site, likely contributing to its infectivity [3]. Reports have also suggested a 10- to 20-fold increase in the binding affinity of SARS-CoV-2 S protein to ACE2, compared to that of a previously encountered SARS-CoV S protein to ACE2 [9].

Exact prevalence, mortality, and other statistics in the current literature are limited due to the variety of presenting symptoms leading to nontesting of positive patients. This effect is potentiated by the heterogeneous availability of testing kits across the globe [3]. Risk factors for mortality due to COVID-19 include hypertension, cardiovascular disease, diabetes, cancer, and obesity [10]. Common presenting symptoms of the virus include fever, cough, olfactory dysfunction, nausea, vomiting, and diarrhea; although, many others have been reported [2]. With much of the early characterization of symptoms relating to the respiratory system, there is a growing interest to understand alternative complications of infection that are increasingly being encountered. More specifically, literature has shown increasing incidence of cardiovascular involvement during disease course and an associated increase in mortality among infected patients [11].

Risk factors of cardiovascular involvement in COVID-19 infection

Disease progression from COVID-19 infection shows symptom manifestations within organ systems beyond the respiratory system. In a previous report, a patient infected with SARS-CoV-2 developed left ventricular dysfunction and pericarditis without any respiratory symptoms [12]. Complications involving cardiovascular system include MI (7.2%–27.8%), arrhythmias (5.9%–16.7%), shock (1.1%–20%), and heart failure (23%) [11]. Coagulation abnormalities and myocarditis have also been reported in various reports [3,11,13]. While the understanding of the novel virus is continuously evolving, the mechanism through which the SARS-CoV-2 virus leads to cardiovascular manifestations is currently suggested to involve the ACE2 transmembrane protein [3]. It is well known that the ACE2 protein is found throughout the body, including the ileum, kidney, adipose tissue, heart, brainstem, lungs, and nasal and oral mucosa, which may explain the symptoms and complications commonly seen with infection [14]. The ACE2 protein is highly expressed in pericytes of blood vessels, and infection could lead to microvascular dysfunction and subsequent acute coronary syndromes [3].

Understanding the risk factors for cardiac involvement in COVID-19 infection is important; previous reports have found an increase in the mortality of infections that are associated with cardiac injury [15,16]. It has been reported that risk factors for cardiac-specific involvement from established COVID-19 infection include many of the aforementioned risk factors for bad outcomes, including DM, HTN, chronic heart failure, previous CAD, atherosclerotic heart disease, and even cancer [11]. Coronavirus-related pneumonia severity has also been implicated as a risk factor for cardiac symptom development in patients with COVID-19 [17].

Another important risk for the development of cardiac abnormalities in COVID-19 patients is the use of particular medications during treatment. The use of antiviral medications has been associated with cardiac manifestations, and antiviral regimens are commonly used during acute treatment of COVID-19 [12]. Hydroxychloroquine and other antiviral therapies frequently used as therapies may cause QTc prolongation and increase the risk for torsades de pointes [13]. Furthermore, coagulation abnormalities associated with COVID-19 infection may, in part, be related to drug–drug interactions that exist between antivirals and antiplatelet or anticoagulant agents [16]. Medications of the angiotensin receptor blocker (ARB) and angiotensin-converting enzyme (ACE) inhibitor classes have also been hypothesized to increase mortality in COVID-19 patients related to the upregulation of ACE2 in patients. It should be noted, however, that there is currently a lack of evidence showing an increase in cardiovascular complications from coronavirus infection with the use of ACE inhibitors or ARB medication [16].

Notable laboratory findings have also been associated with increased cardiovascular involvement during infection. D-dimer elevation of patients was linked with increased hospital death, associating hypercoagulation states from SARS-CoV-2 with elevated inflammatory responses to the virus [3,15]. In

a Chinese cohort, increased levels of NT-proBNP was associated with a need for ICU care, linking heart failure–associated ACE2 upregulation with COVID-19 infection and severity [3]. Elevated levels of troponin I, CRP, ferritin, IL-6, IL-1β, and IFN-γ during cytokine storms can be a predictor of severity of COVID-19 [15,16]. Increased states of inflammation impair the endogenous mechanism of clot dissolution, thereby increasing the risk for complications and possibly explaining the increased frequency of myocardial infarction [15].

Pathophysiology of COVID-19-related cardiovascular infection/injury

Renin–angiotensin–aldosterone system dysregulation

SARS-CoV-2, the virus that causes COVID-19, enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptor [18]. This receptor is expressed in nearly all human organ systems, including the cardiovascular system. ACE2 is widely expressed in several cardiovascular system components, including cardiomyocytes, coronary endothelial cells, and cardiac fibroblasts [19]. The expression levels of ACE2 are highly correlated with heart failure phenotype, as the overexpression of ACE2 can prevent or even reverse heart failure. In contrast, reduced ACE2 expression can accelerate the progression of heart failure [19]. Although this increased ACE2 expression may offer a cardioprotective effect, it may also place these individuals at an increased risk of becoming infected with COVID-19 [20]. This can partially explain why COVID-19 is less prevalent in children with lower ACE2 expression than in adults [21].

Interestingly, studies have shown that SARS-CoV-2 binding with ACE2 leads to a downregulation of ACE2, which overstimulates the renin–angiotensin system to place infected individuals at an increased risk of experiencing cardiovascular injury and thrombotic events [22,23]. Additional studies suggest that this decreased ACE2 expression may also account for the myocardial damage frequently seen with severe cases of COVID-19 [19]. These effects are likely related to the increased activation of angiotensin2 receptor 1 (AT1) following the downregulation of ACE2 receptors, as activation of the AT1 receptors increases blood pressure and has pro-inflammatory consequences, and increases the risk of developing kidney disease [24,25]. Obesity is associated with an overexpression of AT1 receptors, which correlates with the high frequency of obesity among patients admitted to the intensive care unit for COVID-19 [26–28]. Therefore, it is likely that the downregulation of ACE2 and the increased activation of AT1 receptors are essential factors in the detrimental cardiovascular events, including cardiac dysfunction and the progression of atherosclerosis, associated with COVID-19 infections [23,29].

Excessive inflammatory response

Evidence suggests that SARS-CoV-2 may also lead to myocardial dysfunction by inducing an excessive inflammatory response, which results in a dysregulated immune response, cytokine release syndrome (CRS), and eventual cytokine storm [30,31]. The increased cytokine production induces the release of reactive oxygen species (ROS), superoxide anion, and endogenous nitric oxide – all of which contribute to the myocardial damage commonly seen with severe cases of COVID-19 [32]. As the myocardium becomes more damaged, it eventually releases damage-associated molecular proteins (DAMPs), which exacerbate the pro-inflammatory response to injure myocytes further. This vicious, inflammatory cycle results in the cardiomyopathy seen with many severe COVID-19 cases [33,34]. Upon invasion of cardiomyocytes, SARS-CoV-2 triggers the hyperactivation of natural killer cells, macrophages, and lymphocytes, which worsen the myocarditis and cardiomyopathy [32]. Autopsies performed on individuals who had died from COVID-19 presented with an upregulation of proinflammatory genes [35].

Similarly, endomyocardial biopsies performed in patients who had recovered from severe cases of COVID-19 revealed lymphocytic inflammation [36]. Nearly, one-fourth of these individuals presented with ongoing myocardial inflammation three months after COVID-19 diagnosis. These excessive inflammatory responses are hypothesized to be a main contributing factor to deadly cases of COVID-19, where the immune system malfunctions and leads to fatal cardiovascular events [32,37].

Metabolic disarray

As kidney pathology has a functional interface with the cardiovascular system, it is not surprising that renal manifestations are thought to contribute to the short- and long-term cardiovascular events observed in COVID-19 patients [32,38]. When researchers in New Orleans evaluated 287 patients hospitalized for COVID-19, they found that patients with metabolic syndrome were 3.4 times more likely to die from COVID-19 than individuals without metabolic syndrome [39]. These deadly outcomes are often related to cardiovascular events as metabolic syndromes significantly increase a person's risk of developing a spectrum of cardiovascular conditions, such as cardiac dysfunction, myocardial infarction, coronary atherosclerosis, microvascular dysfunction, and heart failure [40]. The underlying mechanisms responsible for kidney and heart disease co-existence include leukocyte infiltration into the myocardium and increased cytokine secretions that contribute to myocardial inflammation, injury, and apoptosis [37,41].

COVID-19 effects on the cardiovascular system and corresponding treatments

Acute cardiac injury

Acute cardiac injury is a broad term that can encompass a number of cardiovascular (CV) issues. As more data are collected in more patients, the case for the association of acute cardiac injury and poor COVID-19 patient outcomes becomes stronger. A meta-analysis of COVID-19 data collected from peer-reviewed publications reported the incidence of acute cardiac injury in COVID-19 cases was 15% and severe cases were almost 5 times more likely to include acute cardiac injury when compared to milder cases [42]. One report collected data on COVID-19 patients in regions of China other than Wuhan (to reduce the confounding factors of an over-stressed healthcare system) [43], found that 75% of patients suffering from acute myocardial injury were severe or critical cases, and they were more likely to require mechanical ventilation and vasoactive drugs.

The term acute (or chronic) myocardial injury applies when cardiac troponin I values are elevated beyond the 99th percentile upper reference limit [44]. In the general population, higher troponin values are associated with higher risk for CV disease and death. However, when adjusted for other risk factors, troponin I levels are correlated with CV disease–related mortality, whereas troponin T levels are correlated with deaths not related to CV disease [45]. In several published studies of Chinese COVID-19 patients, abnormally high cardiac troponin levels were found in 8–12% of study participants [46]. Specifically, an early study published by Guo et al. showed 27.8% of COVID-19 patients had elevated troponin T levels and were more likely to die than those with normal levels [47]. Interestingly, in patients who did not survive, troponin and NT-proBNP (another marker of cardiac injury) levels increased dramatically over the course of their hospitalization. No such significant change in these markers was observed in survivors.

Arrhythmia

Cardiac arrhythmia was an observed complication of the SARS-COV outbreak of 2003 [48] and has emerged as a cardiac complication of the COVID-19 pandemic as well. A 17.6% incidence of cardiac arrhythmia was reported in an early publication of the characteristics of COVID-19 in Chinese patients, making it the second-most reported serious complication, behind acute respiratory distress syndrome (ARDS) [49]. However, a meta-analysis pooling 17 retrospective cohort studies of COVID-19 patients from various nations found that only about 9% of cases included arrhythmias [50]. Antiarrhythmic agents should be utilized in these patients, where appropriate.

There is a risk of QT interval prolongation and arrhythmia associated with the experimental use of chloroquine/hydroxychloroquine for the treatment of COVID-19 infection, or prophylaxis. However, Maneikis, et al. concluded that it would be possible to mitigate the risk of arrhythmia by utilizing an arrhythmia risk management plan [51].

Heart failure

In the previously mentioned meta-analysis [50], the incidence of heart failure was 16.7% – the most common CV complication reported in the included studies. Additionally, in reports on complications in deceased patients, approximately half of those cases included heart failure [52,53]. COVID-19 patients experiencing heart failure should be treated with traditional heart failure medications, as appropriate.

Hypercoagulation

Evidence of coagulopathy is present in an estimated 20–55% of COVID-19 cases admitted for hospitalization [54]. A variety of factors can lead to hypercoagulation in COVID-19, not all directly related to the virus [55]. These include increased risk for deep vein thrombosis as a result of inactivity related to quarantine and isolation, and direct consequences of treatment, including side effects of antiviral therapy [56] and mechanical ventilation [57].

The progression of coagulation dysfunction related to COVID-19 is known as COVID-19-Associated Coagulopathy (CAD). Two indicators of coagulation activity – D-dimer and fibrin degradation product (FDP) – were found to be elevated in an early study of COVID-19 patients [58]. D-dimer is generated during thrombus formation and is released as thrombi break apart. Similarly, FDPs are fragments that are released upon thrombus degradation, but can also occur under normal physiological circumstances; thus, it is the combination of the two markers that suggest pathological thrombus formation. In the same set of patients, prolonged prothrombin time and activated partial thromboplastin time were also observed. All four of these markers were significantly higher upon admission in patients who did not survive and remained elevated during the course of disease progression [58].

Moreover, disseminated intravascular coagulation (DIC) was present in more than 70% of mortal cases in a previously mentioned report from Tang et al. compared to less than one percent of those that survived [58]. However, there was little evidence for DIC in initial presentation, suggesting that a hypercoagulative state develops over time [59]. This DIC data, together with the previously mentioned data noting increasing levels of cardiac injury markers over time (observed in patients that did not survive [47]), suggest that progressive cardiovascular injury during disease course could help predict outcome.

The evidence for hypercoagulation, and the potential for thrombus formation, has led to the recommendation of thromboprophylaxis with low–molecular weight heparin (LMWH), unfractionated heparin (UFH), or the factor Xa inhibitor fondaparinux, for critically ill COVID-19 patients [60].

Myocardial infarction

COVID-19 can, directly and indirectly, injure the cardiovascular system. Direct inflammation and damage are a result of the COVID-19 virus attaching to angiotensin-converting enzyme 2 (ACE2), found in abundance in cardiomyocytes and alveolar cells, among others [61,62]. As COVID-19 attaches to these enzymes, the ability of ACE2 to influence the fluctuation of the renin–angiotensin–aldosterone (i.e., RAAS) system is disturbed, leading to an increased presence of angiotensin II, which is a potent vasoconstrictor. Increased angiotensin II levels further exacerbate the symptoms of stress and inflammation and lead to an increased demand for oxygen, which results in a vicious cycle where the cardiovascular and respiratory systems are trying to compensate for each other. These direct and indirect mechanisms have an apparent additive effect that results in detrimental cardiovascular damage [61].

Individuals with underlying respiratory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, often possess dysfunctional macrophages that may contribute to disease pathogenesis, particularly in diseases that target the lungs, such as COVID-19 [63]. This can cause an increased release of pro-inflammatory cytokines, which reduces lung functionality so that less oxygen is supplied to vital organs, including the heart. Through these direct and indirect mechanisms, the heart is at an increased risk of experiencing permanent damage in vulnerable population groups who become infected with COVID-19, often resulting in myocardial infarction and other cardiovascular diseases [62].

Although there is no consensus on treating these conditions, the primary recommendation is to treat the patient's underlying conditions and any new conditions that may occur, including myocardial infarction. Some medical providers administer low–molecular weight heparins or unfractionated heparin in acutely ill patients to avoid clotting. Further studies have indicated that there may be some benefit to administering fibrinolytic therapy whenever possible over percutaneous coronary intervention (PCI), especially to avoid unnecessary “hardware” to a person that would otherwise not need it [64].

Cytokine storm and heart damage

Beyond just the damage to the cardiovascular and pulmonary systems, COVID-19 may induce severe, long-term damage to a patient's immunological system, particularly related to a hyperreaction referred to as a cytokine storm [65]. Many cytokines respond to the COVID-19 virus, many of which are pro-inflammatory. Some of the primary pro-inflammatory cytokines correlated with COVID-19 infections are ferritin, C-reactive protein, interleukin-6, interleukin-1β, interferon-γ, and tumor necrosis factor-α [62,66,67]. This cytokine storm often results in severe inflammation along with multi-organ failure and is thus hypothesized to play a significant role in the increased mortality associated with COVID-19 infections [62].

For treating a cytokine storm and the excessive levels of pro-inflammatory markers, one focus is to target interleukin-6 as interleukin-6 levels have a position correlational relationship with mortality in COVID-19 patients [68]. Many researchers support the idea that this IL-6 amplification is the primary underlying mechanism responsible for producing the cytokine storm. Therefore, a treatment that focuses on reducing IL-6 levels within the body would be a good candidate for treatment [69]. Tocilizumab is currently FDA-approved for treating cytokine release syndrome and was consequently thought to be a potential treatment option for alleviating the COVID-19-induced cytokine storm [70]. However, current recommendations warn against using IL-6 monoclonal antibodies, such as tocilizumab, as preliminary randomized, controlled trials showed that these medications were incapable of significantly reducing COVID-19 symptoms [71].

Despite the failure of these drugs to reduce the cytokine storm associated with COVID-19, researchers did identify another drug class that showed promise in reducing the risk of developing a severe case of COVID-19 by as much as 50% [72]. It is hypothesized that statins may prevent and/or treat the cytokine storm associated with COVID-19 by inhibiting macrophage recruitment and reducing cytokines' consequent expression [73].

Endothelial dysfunction

Endothelial cell injury plays a significant role in the pathology of COVID-19, particularly within the vascular cell walls [74]. As with the cardiovascular and pulmonary systems, the endothelium possesses high levels of ACE2 receptors, which allow COVID-19 to readily enter the endothelial system [62]. As the endothelial system primarily functions to prevent the passage of harmful substances into our circulatory system, this renders multiple organ systems vulnerable to COVID-19 infiltration and infection [61]. Despite ACE2 serving as the entry point for this virus, ACE2 also has protected against pulmonary infections, indicating that increasing ACE2 is a possible treatment option for COVID-19 infections [75].

Many studies focus on inhibiting viral replication and suppressing the excessive immune response to treat the COVID-19-induced endothelial damage and dysfunction [76]. Further studies have shown significant promise in utilizing rein-angiotensin inhibitors and statins to improve endothelial function and offer protective effects. These drug classes have known benefits on the endothelium, such as quelling inflammation, reversing endothelial tissue damage, and preventing thrombus formation [75]. It is not surprising that statins are currently being evaluated for their efficacy in reducing COVID-19 symptoms associated with endothelial dysfunction, as prior studies have suggested these drugs may be promising treatment options for other viral infections, including viral pneumonia and the influenza virus [73]. These medications should not be stopped at the minimum as there was no noted benefit to discontinuing these medications in hospitalized patients unless there are acute and specific contraindications [75].

Hypertension

Recent studies show that individuals with hypertension are almost equally as likely to develop COVID-19 as normotensive individuals. However, hypertension is still of significant importance in predicting the morbidity and mortality associated with COVID-19 infections. It is one of the most significant indicators that an individual will experience severe symptoms that often result in hospitalization [77].

As the ACE2 receptors are the known targets of the SARS-CoV-2 virus, many providers were initially concerned that various antihypertensive medications, including ACE inhibitors and angiotensin II receptor blockers, would worsen the harmful effects of COVID-19. However, research has shown that

these medications do not exacerbate the symptoms associated with COVID-19 and should be continued as prescribed [78]. Some of these medications show promising effects in reducing the symptoms associated with COVID-19. For example, losartan reduced intracellular degradation of ACE2, resulting in the upregulation of ACE2 receptors [79]. This is noteworthy since increasing ACE2 receptors could help reduce the risk of developing a more severe or lethal form of COVID-19 [62].

Angiotensin II receptor blockers may also reduce COVID-19-associated mortality by increasing blood potassium levels, as hypokalemia is highly prevalent among patients with severe cases of COVID-19 [80]. Furthermore, the ability of these medications to target the renin–angiotensin–aldosterone system may have a two-fold effect that allows for regulation of both blood pressure and the immune system, thus reducing many of the symptoms associated with COVID-19 infections [81].

Hematologic effects of COVID-19

Beyond the previously discussed CAD, hematologic manifestations have been described in some cases of COVID-19 from the earliest reports of the pandemic, including lymphopenia, neutrophilia, and thrombocytopenia. Accumulating data show a correlation between these manifestations and outcome.

Upon admission, Guan et al. found that over 80% of patients presented with lymphopenia [59]. Another study of Chinese patients during the same timeframe found that patients with lymphopenia were more likely to progress to acute respiratory distress [82]. and Wang et al. reported patients were more likely to develop severe disease, and less likely to survive, with declining white blood cell counts [49].

Neutrophilia accompanied lymphopenia in several studies [83,84], and the neutrophil-to-lymphocyte ratio was determined to be an independent risk factor for mortality in hospitalized patients in Wuhan [83]. Moreover, neutrophilia alone was found, similarly to lymphopenia, to be associated with disease severity [85], likelihood to develop ARDS [84], and mortality [86].

In general, platelet count is an independent predictor of both disease severity and survival in intensive care unit patients [87,88]. Thrombocytopenia has been observed in some cases of COVID-19, and low platelet counts are correlated with disease severity and mortality according to a meta-analysis of 9 published reports of COVID-19 patients [89]. Additionally, the presence of severe thrombocytopenia, along with abnormalities in markers for coagulation (D-dimer, FDP, prothrombin time and activated partial thromboplastin time) as mentioned earlier, can lead to DIC in some cases [85].

COVID-19 in heart transplant patients

Many of the studies to date concerning COVID-19 in heart transplant patients postulated that heart transplant patients would have a worse outcome with a COVID-19 infection. However, this correlation does not always hold.

COVID-19 effects on heart transplant patients vary in disease course between different studies. One study followed five heart transplant patients with COVID-19, three of these patients experienced severe disease, and two of these patients experienced moderate disease. The patients who experienced severe disease had received a transplant within six weeks. The severe symptoms included “profound lymphopenia” and “markedly elevated C-reactive protein, procalcitonin, and ferritin.” During this study, the patients underwent endomyocardial biopsies revealing either mild cellular rejection or no cellular rejection. Lastly, within thirty days of admission, the two severe cases were still at the hospital (however, these patients had improved).

In contrast, the other three study participants had been discharged [90]. In a study following twenty-two heart transplant patients who contracted COVID-19, 25% required mechanical ventilation, and 32% died of COVID-19-related complications. Overall, this study found that transplant patients who contracted COVID-19 were at an increased risk of more serious infection [91]. A different study in China tracking heart transplant patients who followed preventative measures showed that these patients had a “less than expected rate of infection” with COVID-19 [92]. Another study was also conducted at the beginning of the pandemic. Still, this time in Germany, noted that heart transplant patients were presumed to be in a high-risk category for severe infection not only related to the chronic immunosuppression but also due to various comorbid diseases in heart transplant patients that are associated

with a bad outcome with COVID-19 infection [93]. This study cited comorbidities associated with the highest mortality in heart transplant patients as being "right ventricular dysfunction, arrhythmias, thromboembolic events, and markedly elevated cardiac biomarkers" [93]. Another study found that although presumed to have a bad course, the solid organ (heart and kidney) transplant patients followed in that study, who were on immunosuppression and who contracted COVID-19, had a mild course [94]. Still, some studies find that the effect of COVID-19 on heart transplant patients is unclear. The effects are especially unclear in patients in the early post-transplant period [90]. Related to the pandemic being less than one-year old, we have only seen the virus's short-term effects, and the long-term effects are still largely unknown.

Although many studies generally presume that heart transplant patients are at a high-risk for a bad outcome with COVID-19 infection due to both chronic immunosuppression and comorbidities associated with a bad disease outcome, the overall effects of COVID-19 seen in the patients in these studies vary (including mild, moderate, and severe disease course). Furthermore, there is no obvious pattern for these differences between the subjects. Also, only the short-term effects of COVID on heart transplant patients are known to date as the long-term effects are yet to be seen.

Conclusion

Disease progression from COVID-19 infection has shown symptom manifestations within organ systems beyond the respiratory system. Although the understanding of the novel virus is continually developing, it is currently proposed that the mechanism by which the SARS-CoV-2 virus contributes to cardiovascular manifestations involves the ACE2 transmembrane protein. The protein ACE2 is highly expressed in blood vessel pericytes, and infection can result in microvascular dysfunction and subsequent acute coronary syndromes. An increasing incidence of cardiovascular involvement during disease course and a related rise in mortality among infected patients have been shown in the literature. Myocardial infarction, arrhythmias, shock, and heart failure are some of the complications affecting the cardiovascular system. Although there is no consensus about the treatment of these conditions, the main recommendation is to address the underlying conditions of the patient and any new conditions, including myocardial infarction, that may arise. In acutely ill patients, some medical practitioners prescribe low–molecular weight heparin or unfractionated heparin to prevent clotting. Further studies have shown that delivering fibrinolytic therapy can be of some benefit. Many studies also focus on inhibiting viral replication and suppressing the excessive immune response to treat the COVID-19-induced endothelial damage and dysfunction.

Declaration of competing interest

Richard Urman reports unrelated research funding from AcelRx and fees from Medtronic, Merck, Pfizer, Heron, and Takeda. Alan Kaye reports fees from Merck. Other authors report no conflicts of interest.

Practice points

- Disease progression from COVID-19 infection has increasingly shown significant symptom manifestations within organ systems beyond the respiratory system.
- Literature shows increasing numbers of cardiovascular involvement during disease course and an associated increase in mortality among infected patients.
- Risk factors for mortality due to COVID-19 include hypertension, cardiovascular disease, diabetes, cancer, and obesity.
- Complications involving the cardiovascular system include myocardial infarction, arrhythmias, shock, and heart failure.
- Studies have shown that SARS-CoV-2 binding with ACE2 leads to downregulation of ACE2, which overstimulates the renin–angiotensin system to place infected individuals at an increased risk of experiencing cardiovascular injury and thrombotic events

Research agenda

- Although many studies presume that heart transplant patients are at a high-risk for a bad outcome with COVID-19 infection due to both chronic immunosuppression and comorbidities associated with a bad disease outcome, the overall effects of COVID-19 seen in the patients in these studies vary
- Although there is no consensus about the treatment of these conditions, the main recommendation is to address the underlying conditions of the patient and any new conditions, including myocardial infarction, that may arise.
- Coagulation abnormalities associated with COVID-19 infection may, in part, be related to drug–drug interactions that exist between antivirals and antiplatelet or anticoagulant agents. Future trials will clarify some controversial current guidelines on how to manage immunosuppression in kidney transplant patients with COVID-19.

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