REVIEW ARTICLE

The cardiovascular implications of COVID-19: A Comprehensive Review

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Abstract

The coronavirus disease of 2019 (COVID-19) is a global medical crisis that has posed immense challenges to the medical fraternity worldwide. COVID-19 is caused by Severe Acute Respiratory Syndrome - Corona Virus - 2 (SARS-CoV-2) that targets the host's Angiotensin Converting Enzyme -2 (ACE2) receptors present in the lungs, heart, blood vessels, kidneys and intestines. Symptoms are primarily respiratory in origin but the disease has the propensity to involve all organ systems quickly to cause multi-organ failure and death. The patients with pre-existing cardiovascular diseases are more prone to contracting infection, and the involvement of cardiovascular system itself has been linked to increased morbidity and mortality in COVID-19 patients. Therefore, learning about the cardiovascular implications of SARS-CoV-2 infection is of paramount importance for the cardiology world at this juncture. Herein, we review the initial literature relevant to SARS-CoV-2 associated cardiovascular pathology, highlighting cardiac manifestations, biomarker utility and therapeutic landscape in the present era of COVID-19.

Introduction :

The emergence of coronavirus disease of 2019 (COVID-19) from Wuhan, China, has resulted in significant morbidity and mortality across the globe since the appearance of first case on November 17, 2019 (1) Given the status of a global pandemic by the World Health Organization on March 11, 2020 (2), COVID-19 continues to pose immense challenges to the medical community worldwide as it has engulfed more than 150 countries, affecting more than 1.5 million people by now and deaths have topped 100,000 (3). COVID-19 is caused by Severe Acute Respiratory Syndrome - Corona Virus - 2 (SARS-CoV-2) that targets the host's Angiotensin Converting Enzyme - 2 (ACE2) receptors present in lungs to cause respiratory symptoms as well as systemic inflammation (4). Since these ACE2 receptors are also abundantly found in cardiomyocytes, the SARS-CoV-2 infection can potentially prompt a cascade of cardiovascular manifestations, notably myocardial injury, myocarditis and arrhythmia, as supported by mounting evidence through multiple studies recently (5,6). The COVID-19 patients with cardiac involvement have adverse prognosis, both in terms of disease morbidity and mortality (7,8,9,10). In addition to the disease itself, the various treatment options being considered for the SARS-CoV-2 infection possibly carry cardiovascular implications. Moreover, there have been questions regarding the use of ACE-inhibitors in COVID-19 patients with the virus receptor site for intracellular entry being the ACE2 receptor (11,12). Therefore, it is of immense importance to learn the pathogenesis, types and severity of SARS-CoV-2 associated cardiac ailments and their impact on overall disease outcomes in COVID-19 patients to manage acute and long-term cardiovascular complications.

Data Collection and Literature Review:

We extensively reviewed the existing literature on the MEDLINE/PubMed and included all the studies that highlighted risk factors, cardiovascular manifestations and outcomes of COVID-19 since the beginning of the pandemic. These included retrospective studies, meta-analysis and case reports that were published in numerous peer-reviewed journals. Understandably, the majority of the studies came from China which was the initial epicenter of the pandemic. In the absence of large scale, randomized clinical trials or prospective studies, and the fact that majority of the data stems from single-center, retrospective studies, the accurate assessment of cardiovascular impact of coronavirus is tedious to gauge. However, given the acuity of the situation and the urgent need to extract the best from the existing data, we endeavored to utilize the available data to come up with this review to contribute to the scientific community.

COVID-19 and pre-existing comorbidities:

Studies so far have shown that patients with pre-existing comorbidities including cardiovascular disease (CVD), diabetes, hypertension and obesity are more at risk to contract SARS-CoV-2 infection than general population (37, 38, 39, 44). Endothelial dysfunction, a severe pro-inflammatory milieu and decreased immunity are potential

explanations which may render the host more susceptible (41). Guan, Wei-jie, et al. studied 1590 confirmed cases of coronavirus and observed that 25.1% of the cohort had at least one of the comorbidities. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%) (40). In another study conducted by Chen N et al in 99 hospitalized patients infected with pneumonia due to SARS-CoV-2, 40% had pre-existing CVD, particularly coronary and cerebrovascular diseases (39). Moreover, the presence of comorbidities is associated with complicated clinical courses as well as adverse outcomes with SARS-CoV-2 infection (7, 44). A meta-analysis by Li B et al. of six studies with 1527 COVID-19 patients showed that the prevalence of hypertension, cardiovascular disease and diabetes was 17.1%, 16.4% and 9.7%, respectively, and patients with these comorbidities were more likely to be admitted to the intensive care units (44). The studies from China have demonstrated that COVID-19 mortality rate was highest among patients with CVD (13.2%) compared to other comorbidities such as cancer, chronic respiratory disease and was disproportionately higher for patients with cardiovascular risk factors such as diabetes (9.2%) and hypertension (8.4%) compared to around 1% for patients without such comorbidities (38). Therefore, exclusive attention must be given to optimize chronic medical conditions in order to decrease the risk of developing COVID-19 infection and to improve the prognosis.

Molecular mechanisms of myocardial injury in SARS-CoV-2 infection:

The pathophysiology and molecular pathways responsible for myocardial involvement in SARS-CoV2 infection are not yet understood, and there are various proposed mechanisms. For instance, there may be both direct pathogen-mediated pathways as well as indirect pathways through inflammation and hypoxia. One potential mechanism involves direct virus-mediated ACE2 receptor pathway. In this case, the SARS-CoV-2 uses the ACE2 receptors for gaining cellular entry; these receptors are present abundantly in cardiomyocytes, pulmonary alveolar epithelial cells, endothelium, kidney and intestines (13, 14). After binding to its receptor, SARS-CoV-2 gets cellular entry via receptor-mediated endocytosis (20, 45, 46). It then uses host's nuclear replicative machinery for viral multiplication. Moreover, the ACE2-related downstream signaling pathway could lead to myocardial injury (4). ACE2 has a role in lung protection via production of anti-inflammatory substances (Ang 1-7 and Ang 1-9), therefore, viral binding to ACE2 receptor deregulates a lung protective pathway, contributing further to viral pathogenicity (20, 46).

Another proposed mechanism involves indirect mode of cell damage through activation of T helper cell response, which then triggers a cytokine storm resulting in systemic inflammation and multi-organ dysfunction (5, 20, 47). Studies have suggested that SARS-CoV-2-infected patients have had high levels of inflammatory markers including interleukin (IL)-1 beta, interferon gamma (IFN-γ), IFN inducible

protein (IP)-10, and monocyte chemoattractant protein (MCP)-1, resulting in a cascade of T helper-1 and helper-2 cell responses. The fact that concentration of certain markers is also noted to correlate with the disease severity, as seen in ICU patients, with SARS-CoV-2 infection further supports this indirect mechanism of cellular injury through hyperactivation of T cell response. For example, those requiring ICU admission had higher concentrations of granulocyte colony-stimulating factor (GCSF), IP-10, MCP1, macrophage inflammatory protein (MIP)-1A, and tumor necrosis factor (TNF)-α, compared to those who never required ICU care, suggesting that the cytokine storm could lead to direct cellular injury, along with impacting disease severity. It was also observed that the plasma IL-6 level was increased dramatically in SARS-CoV-2-infected patients with cardiac injury (16). Furthermore, cytokine storm is also the core pathophysiological mechanism associated with fulminant myocarditis, which has been observed in numerous SARS-CoV-2 cardiovascular deaths. Other indirect pathways involve hypoxia-induced myocardial damage in the setting of severe acute respiratory distress (ARDS) caused by COVID-19 (4).

Cardiovascular manifestations of SARS-CoV-2 infection:

A wide spectrum of cardiac manifestations has been reported with COVID- 19 ranging from mild troponin elevation to severe myocarditis and cardiogenic shock adversely affecting the outcomes. The most reported cardiovascular manifestation is acute myocardial injury, indicated by troponin elevation above the 99th percentile upper reference limit, with or without electrocardiographic and echocardiographic abnormalities (5, 10, 17). An elevation in serum troponin is seen in various forms of myocardial damage caused by SARS-CoV-2 infection including myocardial infarction (plaque rupture or demand ischemia based), myocarditis, heart failure and persistent arrhythmias. Multiple studies, mostly utilizing the high-sensitivity troponin, have observed troponin elevation as a frequent occurrence in patients diagnosed with COVID-19 (5, 6, 8, 9,10,17,18). Shi S et al. demonstrated that elevated high-sensitivity troponin (hs-TnI) occurred in 20% of patients hospitalized for COVID-19 (17). Similarly, Huang et al. reported acute myocardial injury in 12% of the 41 COVID-19 patients while Liu et al. mentioned that in 8% (5, 10).

Heart failure was reported in 23.0% of patients with COVID-19 presentations by Zhou et al. (7). In this study, presence of heart failure was associated with worse survival compared to its absence (51.9% vs.11.7%). Whether the heart failure cases in COVID-19 are a result of new-onset cardiomyopathy or a decompensation of pre-existing systolic or diastolic dysfunction is unclear. Pulmonary hypertension is another important consideration for mechanical ventilation in cases of COVID-19, as it is triggered by ARDS and can result in right ventricular failure.

Another common cardiovascular manifestation described in patients with COVID-19 infection is cardiac arrhythmia. Liu et al. reported heart palpitations as presenting symptom in 7.3% of patients in a cohort of 137 patients admitted for COVID

19 disease (19). In hospitalized COVID-19 patients, cardiac arrhythmia was noted in 16.7% of 138 patients in a Chinese cohort and was more common in ICU patients compared to non-ICU patients (44.4% vs. 6.9%) (6). Although these studies have mentioned arrhythmia, there have been no specifications with respect to type or characteristics. The reported arrhythmia could, in part, be multifactorial and induced by electrolyte disturbance, hypoxia or inflammatory stress secondary to viral infection (20).

Viral myocarditis is also a serious complication of COVID-19 and results in focal or global myocardial inflammation, necrosis, and eventually ventricular dysfunction. A few case reports have observed the initial presentation as a mimicker of acute myocardial infarction, with ST- segment elevation and troponin elevation (42,43). Cardiac catheterization did not reveal critical coronary obstruction and the diagnosis of myocarditis was established based on imaging, either Chest CT (42) or cardiac MR (43). The detection of a global reduction in left ventricular ejection fraction on echocardiogram (versus segmental wall motion abnormalities as seen in STEMI) at presentation was the hallmark in these cases, and the mainstay of treatment was steroids, with clinical recovery after a few days.

Patients with COVID-19 are likely at a higher risk of venous thromboembolism in the presence of venous stasis along with hypercoagulability and endothelial dysfunction secondary to severe illness. Patients with COVID-19 have been shown to have abnormal coagulation parameters, including elevated D-dimer and fibrin degradation products (FDPs). The elevated D-dimer has been shown to independently predict in-hospital deaths in the study (7). A retrospective analysis of 183 patients in China with COVID-19, 21 (11.5%) died, of which 15 (71.4%) had evidence of DIC (51). Those who died had significantly longer prothrombin and activated partial thromboplastin times compared to survivors.

Besides direct cardiovascular effects, COVID- 19 has the propensity to cause negative outcomes by indirectly impacting cardiovascular care. For instance, fear and anxiety during this global pandemic, along with limited access to dedicated cardiac care (due to social factors, lookdowns/curfews in many regions, wide-spread closure of ambulatory clinics etc,) can potentially lead to a delay in seeking care for acute and emergent cardiac issues like myocardial infarction, and can result in severe and fatal complications secondary to delayed presentations. Moreover, cardiac teams around the world are facing logistical and pragmatic challenges while treating such patients in catheterization labs or operating rooms in a timely fashion while limiting exposure.

Role of cardiac biomarkers in predicting Covid-19 outcomes:

In a study conducted by Huang et al, in five out of the 41 patients who had elevated troponin, four were critically ill and required admission to the intensive care unit (ICU), indicative of the severity of clinical symptoms and the serious nature of myocardial injury (5). In another study conducted by Shi S. et al. comprising of 416 patients with COVID-19 in Wuhan, China,

20% had myocardial injury (17), and the mortality rate was much higher among patients with cardiac injury versus those without (42 [51.2%] vs 15 [4.5%]; P <0 .001); moreover, there was a direct correlation between mortality and the magnitude of troponin elevation. The multivariate Cox regression of this study also established independent association of elevated troponin with mortality. However, the eventual cause of deaths was not reported in the study. Similarly, a meta-analysis of 4 studies including a total of 341 patients showed that standardized mean difference of cardiac troponin I levels was significantly higher in those with severe COVID-19 related illness compared to those with non-severe disease (25.6, 95% CI 6.8-44.5) (9). Cohort studies from hospitalized patients in China estimate that acute cardiac injury – which includes not only elevation of cardiac biomarkers to more than 99th percentile of the upper reference limit, but also electrocardiographic and echocardiographic abnormalities, occurs in 7-17% of hospitalized patients with the disease (5,6,7) and is significantly more common in patients admitted to the ICU (22.2% vs. 2.0%, p<0.001) and among those who died (59% vs. 1%, p<0.0001) (7,13), confirming the association of acute cardiac injury with more severe disease and worse outcomes. An important caveat to consider is that elevated troponin occurs both with renal dysfunction (due to diminished troponin excretion), and with severe respiratory distress (due to demand-ischemia), cofounding conditions that were present in all the cohorts of patients that were studied.

Another biomarker that has been studied in COVID-19 is the natriuretic peptide. The natriuretic peptides, B-type or NT-Pro B-type, are markers of myocardial stress and usually elevated in decompensated heart failure. They are also frequently elevated in severe respiratory failure in the absence of clinical heart failure (48). Elevated natriuretic peptides have been reported in patients with COVID-19, with the levels significantly correlating with troponin levels (49) and higher values correspond to disease severity and ICU admissions (50). The cardiac versus non-cardiac origin of the natriuretic peptides have not been delineated clearly in the study population in these studies, and the right heart catheterization would be the way to answer this question.

COVID-19 evolving therapies and cardiovascular effects:

There are various antiviral therapies under investigation as frontline curative measures against COVID-19. Many of these medications are already being used for other disease conditions, including human-immunodeficiency virus (HIV) and hepatitis C virus (HCV) (21, 22). In an attempt to repurpose anti-HCV medications including Ribavirin, Sofosbuvir and Remdesivir for the treatment of SARS-CoV-2 infection, the results have been promising and offer a glimmer of hope (23). Ribavirin, a nucleotide inhibitor, binds to the active site on the RNA-dependent RNA polymerase on SARS-CoV2. It does not have direct cardiovascular toxicity, although it does have known drug-drug interaction with warfarin and can impact its dosing. Remdesivir, is another

investigational agent with broad viral coverage. It is also an RNA polymerase inhibitor and was used during the Ebola crisis, with only modest effectiveness, and is currently under investigation for current COVID-19 crises. It does not have reportedly direct cardiovascular toxicity.

The anti-HIV drug lopinavir/ritonavir inhibits replication of RNA virus and has evidence of a synergistic effect in vitro with ribavirin (24). The cardiovascular adverse effects include QT and PR interval prolongation, particularly in patients who have a baseline abnormality (long QT) or are at risk for conduction abnormalities including those taking other QT prolonging drugs (24). In terms of drug-drug interactions, lopinavir/ritonavir through inhibition of CYP3A, has the propensity to alter concentration of P2Y12 inhibitors (e.g clopidogrel, ticagrelor, prasugrel etc), direct oral anticoagulants (DOACs) and other CYP3A mediated drugs. DOACs such as rivaroxaban and apixaban may require dose reductions or avoidance as their serum concentration will be increased (25,26). On the contrary, the serum concentration of active metabolites of clopidogrel will be decreased with concomitant administration of Lopinavir/ritonavir and is concerning for insufficient platelet inhibition in that setting (27,28). The inverse is true with Ticagrelor, as Lopinavir/ritonavir causes increased serum levels of Ticagrelor, and therefore the concomitant use is not recommended in routine practice (29,30). Lopinavir/ritonavir also increases the serum concentration of statin medications, thereby increasing the likelihood of myopathy and rhabdomyolysis in severe cases (31).

The cytokine storm associated with COVID-19, in part, plays a role in the development of ARDS, fulminant myocarditis and other inflammatory symptoms, and using immunomodulatory therapy to limit this hyperinflammatory response may be effective. The drugs acting through immune modulating mechanisms have also been under study, the most common being chloroquine. Chloroquine has been used as an antimalarial agent beside its use as a maintenance therapy in the autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis etc,. It acts by increasing the endosomal pH required for virus/cell fusion, which prevents viral attachment, and has been demonstrated in vitro to have inhibitory activity in SARS-CoV2 (32, 33). Unfortunately, chloroquine use also carries some cardiovascular toxicities, manifesting as conduction abnormalities thought to be due to intracellular inhibition of lysosomal enzymes in the cardiomyocyte (34). Chloroquine is also associated with risk of increasing the QT interval and development of Torsades de pointes in patients with electrolyte abnormalities or with concomitant use of QT prolonging agents. In addition, due to inhibition of CYP2D6, chloroquine affects beta-blockers metabolized via CYP2D6 (such as metoprolol, carvedilol, propranolol, or labetalol) and results in increased serum concentration requiring close monitoring for heart rate and blood pressure.

Lastly, there has been a concern for use of ACE inhibitors in COVID-19 patients. Given

that ACE2 receptor is the mechanism of entry for SARS-CoV2, some data suggest that ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) may up-regulate levels of ACE2 receptor, thereby increasing susceptibility to the virus (4). On the contrary, there are studies that show ACE2 negatively regulates the renin-angiotensin system by inactivating angiotensin II and likely plays a protective role against the development and progression of acute lung failure (35, 36). Thus, due to insufficient data to establish any link between ACE-I/ARB therapy and SARS-CoV-2 infection, the therapeutic implications for ACEi/ARB therapy during COVID-19 infection is unclear. The current recommendations from AHA/ACC/ESC are to continue the use of ACE-I/ARB as clinically indicated as per the guideline-directed therapeutic protocols, and to avoid the initiation of ACE-I/ARB in the absence of a compelling recommendation.

Conclusion:

The COVID-19 pandemic has resulted in significant health concerns across the globe. Initially seen as an infectious process predominantly involving the respiratory tract, there is now an increasing awareness and growing concern of concomitant cardiac involvement that has been linked to worse prognosis and increased mortality. The myocardial injury, indicated by troponin elevation, has been used as a predictor of disease prognosis in some studies, and so has been the case with the utilization of BNP. The spectrum of cardiac involvement in COVID-19 has ranged from mild troponin elevation to fulminant myocarditis.

At this time, as we are feverishly gleaning more insight into the disease process and the associated cardiovascular ramifications. In the coming weeks and months, as COVID-19 research endeavors heighten, we will accrue greater familiarity with this disease process and its mechanisms of cardiovascular involvement, which will form the basis for future therapeutic advancements.

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