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Review Article

Cardiovascular Co-morbidity in COVID 19 Disease

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ABSTRACT

At present, we are in the middle of a global pandemic due to COVID 19 disease caused by SARS-CoV-2 viral infection. It has now spread virtually to every corner of the globe. Medical professionals are faced with the challenge of managing diverse clinical manifestations and multisystem involvement of this infection. Although respiratory system is mainly involved COVID-19 disease, there have been diverse manifestations with the cardiovascular (CV) problems that posing unique therapeutic challenges. Clinically, a patient may have features of myocarditis, heart failure, acute myocardial infarction, arrhythmia, and vascular thrombosis. Of these manifestations, the most common mechanism implicated is direct myocardial injury, whereas systemic inflammation, oxygen supply-demand mismatch, plaque rupture have also been suggested. Furthermore, current available data suggest cardiovascular related manifestations lead to increased morbidity and mortality. Also, patients with underlying cardiac conditions are more prone for severe disease and death. Although there are limited treatment options available for COVID-19 currently, it is imperative that the potential cardiovascular implications of these therapies are to be considered in these patients. There is need to review current available information regarding the implication of cardiovascular co-morbidity in COVID-19 disease so that we have updated and better understanding in this global problem. This review highlights the manifestations, pathophysiological mechanisms for cardiovascular manifestations of COVID-19 and address the specific concerns of cardiac patients regarding medications and further management.

Keywords: Coronavirus, Myocarditis, Heart failure, Arrythmia

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INTRODUCTION

The world is presently facing the challenge of the global pandemic caused by the novel coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), which results in a disease commonly known as Coronavirus disease 2019 (COVID-19). This disease started in Wuhan, China in December 2019. Since then, COVID-19 has spread rapidly worldwide affecting more than 200 countries and territories, with an unprecedented burden not only on public health as well as social and economic activities. The exceptional increase in the number of patients has overwhelmed health- care systems in numerous countries across the world.[1] On March 11, 2020, the World Health Organization (WHO) declared the disease a global pandemic in view of the immense health burden and complete disruption of normal daily activities it has caused to world population.

SARS- CoV-2, is a member of the same Beta-corona virus genus that includes two other coronaviruses which have caused previous epidemics in recent times, namely severe acute respiratory syndrome coronavirus and middle east respiratory syndrome coronavirus.[2,3] However, in addition to respiratory symptoms, SARS- CoV-2 infection can trigger a cytokine storm in minority of cases, overproducing pro- inflammatory cytokines and chemokines such as tumor necrosis factor- α, interleukin- IL and interleukin-6 by the immune system, resulting in multiorgan damage[4]. Furthermore, COVID-19 can induce pro coagulation state in a substantial proportion of patients, which can lead to thromboembolic events like deep vein thrombosis and pulmonary embolism.[5]

We now have evidence that the clinical spectrum of COVID-19 is quite varied. It may cause asymptomatic infection or mild upper respiratory tract illness to severe viral pneumonia with severe hypoxia.[6] Though, it is clear that respiratory tract is the primary target for SARS-CoV-2 virus, multisystem involvement is common. Cardiovascular involvement has been documented in different studies and have shown that cardiac involvement up to 40% of patients dying from COVID-19 disease[7]. Recent evidence also suggests acute myocarditis, acute coronary syndrome, arrythmias and exacerbation of heart failure with significant impact on clinical outcome.[8]

Similarly, patients having pre-existing cardiovascular disease are found to have an increased risk of severe infection and tend to have worse clinical outcomes. Specifically, elderly patients with cardiovascular disease, diabetes and hypertension have more adverse outcome rate as shown in one study with mortality rate of 10.5% reported in cardiac patients as well as mortality of 7.3% and 6.0% for diabetic and hypertensive patients, respectively.[9]

Though at present, we do not have complete understanding of the mechanisms underlying COVID-19-related myocardial injury, this review aims to present recent available evidences regarding various aspects cardiovascular disease in relation to COVID-19.

Figure1: Flow diagram of study selection

Literature search performed using the PubMed and google search engines

Used keywords as “COVID-19”, “SARS-CoV-2”, “comorbidity”, “cardiovascular disease” “prevalence”,

The excluded studies: (1) that did not include information on clinical outcomes, (2) included only mortality outcomes (3) that did not have description on age of the patients.

Full articles of potentially eligible studies were acquired and assessed, then selected the studies included in our review.

CARDIOVASCULAR MANIFESTATION OF COVID 19

Many viral infections can cause involvement of myocardium by different mechanism. Cardiac involvement has been reported with previous corona infections like SARS causing heart failure, arrhythmias, and sudden death.[10] Similarly, COVID-19 can have spectrum of cardiovascular manifestation as described below.

Acute myocarditis: It is one of the common cardiovascular complication in COVID-19 manifested by elevation of high-sensitivity cardiac troponin I and is commonly defined clinically as the elevation of cardiac troponin level above 99th percentile of upper reference limit.[11] The incidence of acute myocardial injury has been reported to be around 8% to 12% in earlier studies.[12] The spectrum of symptoms may vary from mild symptoms such as mild chest pain, dyspnea and fatigue to more severe symptoms like heart ventricular failure, cardiogenic shock, arrythmia, and sudden cardiac death with fulminant myocarditis. Overall, patients with evidence of myocarditis tend to have poorer prognosis.

In one of early study, Lippi et al[13] described it to occur on 8 to 12 percent in infected patients. In a similar

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single-center case series of 138 patients, 36 patients who required ICU admission, the level of creatine kinase (CK)-MB and troponin I were significantly higher.[14] These studies have found that increased troponin levels were associated with higher mortality in the patients with or without previous cardiovascular co morbidity. Another study done in Wuhan with a total of 82 out of 416 hospitalized patients showed increased surrogate markers for myocardial injury and the mortality rate was higher in this group of patients even after adjustment for age and other comorbidities.[15] The patients admitted to ICU or having severe/fatal illness have several-fold higher likelihood of troponin elevation whereas it was very low (2%) in patients having mild illness.

Heart failure: Another important manifestation of COVID-19 disease is either new development or decompensation of heart failure symptoms. One study from China reported features of heart failure was present in 52% of patients who had died and only 12% in those patients who had recovered.[16] The etiology of acute or decompensated heart failure in COVID-19 is multifactorial and has not been adequately studied.[17] Since the patients are likely to be elderly with pre- existing comorbidities like coronary artery disease, hypertension and diabetes, it might be the result of an exacerbation of these pre- existing conditions. In particular, high fever, tachycardia, excessive hydration and impaired renal function might trigger heart failure with preserved ejection fraction. Acute myocarditis and myocardial infarction triggered by COVID-19 can also aggravate pre- existing heart disease leading to decompensated heart failure. Rarely, it is also documented that the immune system response to infection might trigger the development of stress- induced cardiomyopathy or cytokine- related myocardial dysfunction, as with sepsis- associated cardiac dysfunction.[18,19]

Acute Coronary Syndrome (ACS): Currently evidence suggests that incidence of ST segment elevation myocardial infarction (STEMI) in the setting of COVID 19 disease is likely low though there are no enough statistics. In a case series from Italy involving 28 patients with COVID-19 and ST segment elevation myocardial infarction, coronary angiography showed that 17 patients had evidence of a culprit lesion requiring revascularization.[20] In that study, 24 of these 28 patients had not yet received a positive test result for COVID-19 before intervention. These observations suggest that COVID-19 can cause ACS even in the absence of substantial systemic inflammation. However, actual incidence of ACS in COVID-19 patients is still not known. The number of cases of acute myocardial infarction among patients with COVID-19 might be underestimated in earlier observation considering the overburden health facilities and reluctance of patients to go to hospital. This observation is supported by the finding that patients with myocardial infarction seeking urgent hospital care declined more than 50% during the peak of the COVID-19 epidemic, as reported in an extensive global survey by the European Society of Cardiology.[21]

Arrythmias: Both benign and life-threatening arrhythmias including sudden cardiac arrest are common manifestations of COVID-19 disease. Palpitations have been reported to be the main presenting symptom of COVID-19 in patients even without a fever or cough.[22] In a study of patients with COVID-19 in Wuhan, China, cardiac arrhythmia was reported in 17% of all patients including 44% of patients in the ICU though specific types of arrhythmia were not mentioned.[23]

The most commonly reported arrhythmia in COVID-19 disease is symptomatic or asymptomatic tachycardia though bradycardia has been also reported.[24] However, the exact role of viral infection to cardiac arrhythmias remains uncertain. Arrythmia usually occur in the setting of acute myocarditis, myocardial ischemia and in critically ill patients with hypoxia and shock.[25] Other mechanisms that may trigger or aggravate arrhythmias include electrolyte disturbance, adverse effects of therapies (eg, chloroquine/hydroxychloroquine and azithromycin) that prolong QT interval with potential development of polymorphic ventricular tachycardia (VT) and fever which may unmask cases channelopathies such long QT syndrome.[26]

Vascular thrombosis: Thrombotic complications are very common and can occur as high as 31% in critically ill COVID-19 patients.[27] The spectrum of vascular thrombosis include deep vein thrombosis (DVT) pulmonary embolism (PE) and large vessel cerebrovascular accident (CVA), especially among young adults.[28] Klok et at[27] described pulmonary embolism as the most frequent thrombotic complication despite the use of thromboprophylaxis, especially among ICU patients. Interestingly, thromboembolic events can be seen at any stage of the infection even in noncritically ill patients.[29] Though, exact pathogenesis of vascular thrombosis is not clear, potential mechanisms may include disseminated intravascular coagulation, endothelial injury, stasis secondary to immobility and activation of pro-coagulation pathway activation.[29]

Recently, COVID-19 associated coagulopathy has

been identified as a distinct entity. It differs from sepsis-induced coagulopathy and disseminated intravascular coagulation in that there is minimal thrombocytopenia or increased prothrombin time as compared to the more significant changes to latter causes.[30]

MYOCARDIAL INJURY MECHANISM

Several mechanisms are thought to be responsible for the myocardial injury. One of the major mechanism described is direct myocardial injury due to SARS-CoV-2 virus entering human cells by binding to angiotensin-converting enzyme 2 (ACE2), a membrane bound aminopeptidase which is highly expressed in heart and lungs.[31] ACE2 plays an important role in neurohumoral regulation of cardiovascular system. This binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signaling pathways, leading to acute myocardial and lung injury.[31,32] Systemic inflammation in severe COVID-19 infection which are characterized by acute systemic inflammatory response and cytokine storm, can also result in injury to multiple organs including heart. Studies have shown high circulatory levels of proinflammatory cytokines in patients with severe/critical COVID-19 patients.[33]

Similarly altered myocardial oxygen demand-supply mismatch due to increased cardiometabolic demand coupled with hypoxia caused by acute respiratory illness can also lead to acute myocardial injury.[34] Plaque rupture and coronary thrombosis due systemic inflammation as well as increased shear stress due to increased coronary blood flow and prothrombotic state further increases the risk of myocardial injury. Adverse effects of various therapies including antiviral drugs, corticosteroids, and other therapies aimed at treating COVID-19 can also have deleterious effects in heart. Electrolyte imbalances particularly hypokalemia, due to interaction of SARS-CoV-2 with renin-angiotensin-aldosterone system increases vulnerability to various tachyarrhythmias.[35]

CARDIOVASCULAR COMORBIDITY IN COVID-19

We now have persistent evidence that patients with pre-existing cardiovascular conditions have more severe disease with worse clinical outcomes.[36] Various cardiovascular risk factors also adversely affect prognosis of these patients, although they do not seem to increase likelihood of developing the infection.

A large meta-analysis from China which includes six published data involving 1527 patients with COVID-19 reported prevalence of diabetes, cardio-cerebrovascular disease and hypertension as 9.7%, 16.4% and 17.1% respectively.[37] Although the prevalence of diabetes and hypertension was same as in the Chinese general population, the prevalence of cardio-cerebrovascular disease was considerably higher in this study. The study also found presence of diabetes, cardio-cerebrovascular disease and hypertension was associated with two to three times increased risk of severe disease or requiring intensive care.

A similar trend increased comorbidity has been reported in other countries. In a study done in Italy found 49% of patients had hypertension, 21% had preexisting cardiovascular condition and 17% had diabetes.[38] Another report 393 consecutive patients hospitalized in New York, USA, up to 50% of patients had hypertension, 36% had obesity, 25% of patients had diabetes and 14% of patients had coronary artery disease .and incidence was even higher in ventilated patients.[39]

MANAGEMENT OF ACUTE CORONARY SYNDROME PATIENT IN THE SETTING OF COVID-19

As described earlier, acute coronary syndrome including ST-elevation myocardial infarction (STEMI) and non- ST-elevation myocardial infarction (NSTEMI) can occur in subset of patients with COVID-19 disease due to plaque instability or secondary to demand ischemia (hypoxia due respiratory failure, fever and tachycardia secondary to sepsis).[40] Coronary artery involvement impairing blood flow produced by microangiopathy due to systemic vasculitis or microembolization resulting from disseminated hypercoagulability has been described.[41]

The management of STEMI has been particularly difficult due to multiple causes of delay for a primary percutaneous coronary intervention, including dilemma to determine whether STEMI or COVID-19 is the primary problem. A small study evaluating primary PCI calculated the time from onset of symptoms to medical contact to be a median of 318 min as compare to 82.5–91.5 min in the previous year prior covid era. Similarly, the door-to-device time was almost 30 min longer in the same study.[42] This increase in the door to balloon time would invariably increase in one year mortality in STEMI. Recent statements by the American College of Cardiology and Interventional Council and Society for Cardiovascular Angiography and Intervention regarding the management of STEMI during the COVID-19 pandemic, has stated that primary PCI should remain as the standard care and fibrinolytic therapy reserved only for patients with relative

contraindications.[43]

NSTEMI patients with suspected or confirmed COVID-19 should be risk stratified and managed by aggressive medical management until further plan is made. High-risk patients or hemodynamically unstable patients should be managed by early invasive strategy (< 24 h) and non-invasive or medical approach can be reserved for low-risk patients according to recent guideline.[43]

MEDICATIONS IN COVID-19 AND CARDIAC IMPLICATIONS

Various trial of therapeutic agents have been employed to treat patients with COVID-19 which is beyond the scope this review. We focus on commonly used drugs that have been purposed and used to treat this disease emphasizing cardiovascular outcome.

Recent studies found no benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcome for COVID-19.[44] They were rather associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias. Complications of the drugs include severe cardiac arrythmias including polymorphic VT (Torsade de Pointes), long QT syndrome, and increased risk of sudden death.[45]

Prophylaxis with low-molecular-weight heparin (LMWH) should be offered the patients who are admitted and have at least moderate disease, if not contraindicated. In a study involving 449 patients with severe COVID-19, anticoagulation was associated with lower mortality in patients even with markedly elevated d-dimer.[46] The use of unfractionated heparin is recommended with renal failure, which is a contraindication to LMWH. Heparin also have anti-inflammatory effects that reduces myocardial inflammation and may have antiviral effects.[47]

Given the widespread use of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs) in cardiac patients and recognizing role of ACE2 receptors as a co-receptor for viral entry; there has been some concern about of these medications in COVID-19 patients. But the current evidence does not support adverse outcome of these medicines. Zhang et al[48] found a lower risk of all-cause mortality with inpatient use of ACEIs/ARBs compared to non-users. Jarcho et al[49] also stated in their study no evidence of increased risk of infection or mortality in the patients who continued on these medications. Based on available data, the major society guidelines have recommended against stopping ACEIs/ARBs in patients already taking these medications, or initiating these medications in newly diagnosed patients.[50]

CONCLUSION

In conclusion, patients with underlying cardiovascular disease are at higher risk than general population in COVID-19 disease. Patients with underlying cardiac condition may develop acute myocarditis, aggravation of heart failure, arrythmias or even sudden cardiac death during the course of COVID -19 disease. We should encourage known cardiac patients to continue their cardiac medications particularly ACEIs/ARBs as there are no evidence, they cause adverse outcome in COVID-19 disease.

We would continue to learn key new insights about pathogenesis and therapeutics from current ongoing clinical trials. This will evolve over time to further improve the favorable outcomes of the patients during this pandemic. It is therefore highly anticipated that the future studies specifically address the mechanisms, clinical presentation and outcomes of various cardiovascular conditions in COVID-19 patients.

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