COVID-19 and its cardiovascular complications: A comprehensive review

Pavitra Sharma
Department of Zoology Deshbandhu, College, University of Delhi, India
Corresponding author email: skaushik090719@gmail.com

Sunny Kaushik
Fortis Escorts Hospital Faridabad Haryana, India

Abstract---COVID-19 (Coronavirus-19), a life threatening infectious disease caused by the novel single-stranded RNA enveloped Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). The first case of COVID-19 was reported in Hubei province of China on December 8, 2019. The reported cardiac injury could be a result of direct viral invasion of cardiomyocytes with consequent unopposed effects of angiotensin II, increased metabolic demand, immune activation, or microvascular dysfunction. Thromboembolic events have been widely reported in both the venous and arterial systems and therefore have attracted intense interest in the underlying mechanisms. Therefore, a particular attention should be paid towards cardiovascular protection in COVID-19 patients who develop acute cardiovascular syndromes during hospitalization, and/or permanent/semipermanent sequelae after recovery from COVID-19. These conditions definitely require careful clinical assessment, treatment and close follow-up to avoid short-term and long-term complications. Hence; the present review aimed of highlighting comprehensive data in relation of cardiovascular complications of COVID-19.

Keywords---COVID-19, Cardiovascular, Heart.

Introduction

On 31 December 2019, WHO was informed about the cases of pneumonia of unknown cause in Wuhan City, China. On 7 January 2020 a novel coronavirus was identified as the cause by Chinese authorities and was temporarily named as “2019- nCoV”. Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe but this new strain of coronavirus has not been previously identified in any diseases. This novel coronavirus (nCoV) started causing misery in human. The new virus was finally named the “Severe
Acute Respiratory Syndrome Coronavirus 2 (SARS–CoV-2)”. On the 31st of January 2020, the WHO announced that COVID-19 was labeled as Public Health Emergency of International Concern (PHEIC).\(^1\)

Because of the rapid increase in the number of such cases outside China, the outbreak was announced as pandemic on 11 March 2020, by WHO Director-General Dr Tedros Adhanom Ghebreyesus. By then, approximately 118 000 cases had been reported in 114 countries, and 4291 deaths had been recorded. By mid-March 2020, the WHO European Region had become the epicentre of the epidemic, reporting more than 40% of globally confirmed cases. As of 28 April 2020, 63% of global mortality from the virus was from the Region.\(^1\)

Based on the epidemiologic survey and studies, mostly infected individuals had a history of close contact to a patient who had 2019-nCoV infection or a history of travel from Wuhan City or Hubei province, China. The incubation period is approximately 3–7 days. The symptoms of 2019-nCoV infection were nonspecific. However, the most common symptoms were dry cough, onset of fever and generalized weakness. Some patients developed headache and/or myalgia, but upper respiratory symptoms such as runny nose were rare. Diarrhea was often identified, which had been reported 10.6% in SARS and up to 30% in MERS. More 50% of patients developed shortness of breath, the median duration from disease onset to dyspnea was 8 days. If the Patients infected with 2019-nCoV were not treated timely and properly then they used to develop acute respiratory distress syndrome (ARDS), followed by septic shock, refractory metabolic acidosis and coagulation dysfunction.\(^2\)–\(^7\)

Though respiratory failure is the primary cause of mortality but the cardiovascular system is also affected severely by this virus. Increased mortality was observed in the COVID-19 patient with preexisting cardiovascular disease and cardiovascular injuries, including myocarditis\(^36\), cardiac rhythm abnormalities, endothelial cell injury, thrombotic events, and myocardial interstitial fibrosis\(^37\). The underlying pathophysiology of COVID-19-associated cardiovascular complications is not fully understood, although direct viral infection of myocardium and cytokine storm\(^38\) have been suggested as possible mechanisms of myocarditis.\(^8,35\)

**Epidemiology**

**China**

The involvement of cardiac factors was reported early in the pandemic in certain reports. A study of 187 patients treated in a Wuhan hospital between January 23 and February 23, 2020, suggested that 35% had existing cardiovascular comorbidities such as coronary disease, hypertension, and cardiomyopathy, and 28% had myocardial injury indicated by elevated troponin T levels. Other Chinese reports found rates of baseline cardiovascular disease ranging from 5% to 16%, hypertension ranging from 15% to 31%, coronary artery disease of 11%, and diabetes of 10%.\(^9,10\)
World Scenario

Beyond China, even higher rates of these comorbidities have been reported across the world. A retrospective case series from Italy presented results that out of 1,591 critically ill patients with COVID-19 who were admitted to the intensive care unit (ICU), 49% had hypertension, 21% had cardiovascular disease, and 17% had diabetes. As reported in New York between the period of March 2 and April 1, 2020, more than 1150 adults with COVID-19 were admitted to two hospitals and 257 were critically ill. Out of these, 82% had at least one chronic illness, the most common of which were hypertension (63%), obesity (46%), diabetes (36%), and heart disease (19%). In New York approximately 5700 patients with COVID-19 admitted to 12 hospitals, the prevalence of hypertension, diabetes, and coronary artery disease was 57%, 34%, and 11%, respectively.11-13

Mechanisms of Cardiac Damage in COVID-19

Multiple mechanisms have been suggested for cardiac damage, based on studies conducted during the previous SARS and MERS epidemics and the ongoing COVID-19 epidemic.14, 15 Part of the systemic inflammatory response in severe COVID-19 is the release of high levels of cytokines (known as cytokine release syndrome) that can injuring multiple tissues, including vascular endothelium and cardiac myocytes.15-19

Cytokine Release Syndrome

Cytokine release syndrome seems to occur in patients with severe COVID-19 infection. Many pro-inflammatory cytokines are significantly elevated in severe cases, including interleukin (IL)-2, IL-10, IL-6, IL-8, and tumor necrosis factor (TNF)-α. Cytokines play a very important role in case of viral infection. Cytokines try to combat with the virus (phase 1) and during ongoing severe inflammation (phase 2), resulting in acute respiratory distress syndrome (ARDS) and other end-organ damage.18-20

Direct Myocardial Cell Injury

The interaction of SARS-CoV-2 with ACE2 alters the ACE2 pathways which results in acute injury of the lung, heart, and endothelial cells. It has been reported that SARS-CoV2 might directly infect the myocardium, causing viral myocarditis. However, in most cases, myocardial damage seems to be caused by increased cardiometabolic demand associated with the systemic infection and ongoing hypoxia which is caused by severe pneumonia or acute respiratory distress syndrome (ARDS).18

Acute Coronary Syndrome

The main cause of acute coronary syndrome is plaque rupture. In this disease the systemic inflammation and catecholamine surge inherent takes place. Coronary thrombosis has been identified as a possible cause of acute coronary syndrome in COVID-19 patients.21-23
Other Possible Mechanisms

Certain medications such as antiviral medications, corticosteroids, and immunological agents may have cardiotoxic side effects. Electrolyte disturbances occurring during critical illness can cause arrhythmias in patients with cardiac disease. The hypokalemia may get developed in patients with COVID-19, because of the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system. Hypokalemia is the prevalent cause to increase the vulnerability to different types of arrhythmia.18

Myocarditis

Myocarditis is an inflammatory disease of the myocardium that includes a wide range of symptoms like chest pain, fatigue, swelling of legs, ankle and feet, arrhythmias and other flu like symptoms. In order to diagnose the disease, the histological, immunological, and immunohistochemical criteria (called the Dallas criteria) are currently used. According to the Dallas criteria, acute myocarditis is defined as an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes however the ischemic damage may or may not be associated with coronary artery disease. Different infectious and noninfectious triggers can cause myocarditis, although viral infections by Coxsackie B virus, adenovirus, parvovirus B19, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6 are the most commonly identified causes. Additionally, postmortem heart biopsies have shown the presence of myocarditis in some HIV-infected patients.19

However, SARS-CoV and MERS-CoV belong to SARS-CoV-2–related coronavirus family, have also been reported to cause myocarditis. In 1980, Coronavirus-related myocarditis was first reported in a 43-year-old man who developed an upper respiratory tract infection and was hospitalized in Helsinki because of prolonged fever, chest pain, and tiredness. In addition to upper respiratory infection, this patient also developed myocarditis. The occurrence of a significant increase in coronavirus-specific antibody observed in his blood tests suggests that in addition to upper respiratory infection during initial, coronaviruses can cause subsequent myocarditis.19,35

In the earlier studies of SARS-CoV-2 infection, the prevalence of myocarditis complication in COVID-19 patients is not clear. It has been demonstrated that elevations in cardiac enzymes and alterations in ECG and echocardiography results in acute myocardial injury in COVID-19 patients. However, only a small number of these studies provided endomyocardial biopsy (or in some cases autopsy) results to distinguish between sterile myocardial damage and myocarditis.19

Myocardial infarction

Report says that various viral infections can cause a systemic inflammatory response syndrome and therefore increases the risk of plaque rupture and thrombus formation which consequently results in either an ST-elevation MI or non-ST-elevation MI39,40. In a study of 75 patients hospitalized with SARS, it was
observed that acute MI was the cause of death in two of five fatal cases. There is also a remarkable association between acute MI and influenza. It has been reported that the incidence ratio of acute MI within 7 days of influenza infection was 6.1 (95% CI: 3.9 to 9.5). Although evidence of type I MI in patients with COVID-19 have not yet been published. Treatment of ACS in COVID-19 should be according to the updated Society for Cardiovascular Angiography and Interventions guidelines.20-24, 31-34, 39,40

Severe respiratory viral infections cause hypoxaemia and vasoconstriction leading to decreased oxygen delivery to myocardium as well as the haemodynamic effects of sepsis with increased myocardial oxygen demand. This supply and demand mismatch may lead to sustained myocardial ischemia in patients with underlying coronary artery disease. However, a rise and/or fall of hs-cTn is not sufficient to assure the occurrence of acute MI as seen in MI with non-obstructive coronaries, even in the absence of COVID-19. Therefore, clinical judgement, symptom/signs, ECG changes, and imaging studies should be taken into consideration while diagnosing acute MI. 20-24, 31-34

**Myocardial injury with Disseminated intravascular coagulation (DIC)**

DIC is a life-threatening condition present in 71.4% (15/21) of non-survivors with COVID-19 and 0.6% (1/162) of survivors. DIC is a marker of severe sepsis, DIC can lead to multiorgan damage through thrombosis, reduced perfusion, and bleeding. It has been observed that DIC has been inculpated in focal necrosis of the myocardium, the thrombosis of coronary arteries (epicardial vessels and microvasculature), and severe cardiac dysfunction41,42. In a recent report the correlation of Myocardial injury with DIC has been observed in two critically ill patients with COVID-19. Both patients had remarkable elevated Tn and brain natriuretic peptide. However, Tn and brain natriuretic peptide were normalized after treatment with heparin, mechanical ventilation, and antiviral agents. 20-24

**Dysrhythmias**

Palpitations may be a presenting symptom in over 7% of patients with COVID-19. A wide range of dysrhythmias have been observed in patients with COVID-19 infection. Because of multiple, simultaneous causes such as hypoperfusion, fever, hypoxia, anxiety, etc., patients with COVID-19 develop sinus tachycardia. One report reveals that dysrhythmias were present in 17% of hospitalized and 44% of ICU patients with COVID-19. Studies found that dysrhythmias may occur in the setting of viral illness due to hypoxia, inflammatory stress, and abnormal metabolism43. If dysrhythmias are associated with an elevation in serum troponin, the clinician should consider myocardial injury, acute myocarditis, and ACS in the differential diagnosis.25-28

**Venous thromboembolic event**

Patients with COVID-19 are also at a high risk of VTEs44. The potential contributing factors to the increased risk of VTE are systemic inflammation, abnormal coagulation status, multiorgan dysfunction, and critical illness. Studies suggest significant coagulation pathway abnormalities in patients with COVID-19,
including elevated D-dimer\textsuperscript{45}. In a study of 25 patients with COVID-19, it was found that an elevated D-dimer was present in all 25 patients with a median of 6.06 micrograms/ml, and at the same time 10 patients were having a pulmonary embolism (PE). A median D-dimer level of 11.07 micrograms/ml was observed in Patients with confirmed PE. Several studies suggest that, in COVID-19-infected patients, the level of D-dimer greater than 1 μg/mL was associated with an increased risk of death during hospitalization (odds ratio 18.4). Other study suggests that anticoagulation, mainly with low molecular weight heparin, is associated with reduced mortality in severe COVID-19 infections or those with D-dimer level greater than six times the upper limit of normal.\textsuperscript{25-28}

**Medication interactions**

Various newly studied medications interact widely with other cardiovascular drugs, such as antihypertensives, antiarrhythmics, anticoagulants, antiplatelets, and statins. These medications include antivirals (e.g., remdesivir, ribavirin, lopinavir/ritonavir, favipiravir), antimalarials (e.g., chloroquine, hydroxychloroquine), azithromycin, corticosteroids, and biologics (tocilizumab). It has been observed that in the patient with baseline QT prolongation, Lopinavir/ritonavir may cause QT and PR prolongation. the same result is observed in those taking medications which can cause QT prolongation. Studies suggest that these medications also interfere with anticoagulant medications, antiplatelet agents, and statins. It has been found in several studies that chloroquine and hydroxychloroquine affect the intracellular pH, resulting in electrolyte abnormalities and consequently cardiotoxicity and prolonged QT intervals; and they may also interact with antiarrhythmic agents. Electrolyte derangements, fluid retention, and hypertension was also observed in case of Methylprednisolone.\textsuperscript{28-30}

**Conclusion**

A number of published reports, case studies and series, and other meta-analysis have shown that nCoV-19 infection not only worsen and/or increase cardiovascular complications, but also makes the patient more susceptible to such life-threatening infection. Studies have also reported that several anti-CoV-19 drugs have severe side effects on cardiovascular system. To understand the detailed mechanisms of such a complex issue, an elaborate and extensive study of molecular pathogenesis of cardiovascular complication in CoV-19 infection is required. This understanding and information will definitely help in developing a safer and effective cardioprotective anti-nCoV-19 drugs.

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