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Review Article

COVID-19 and Cardiovascular Diseases

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ABSTRACT

Pandemic COVID-19 is a global issue which affected almost 213 countries with definite cases of 20,542,666 across the world as reported by World Health Organization on August 12, 2020. It causes severe acute respiratory syndrome and mainly invades the lungs through angiotensin-converting enzyme 2 (ACE2) receptor. These ACE2 receptors are also found in heart and are reason for serious cardiovascular disease including myocardial injury. This virus can persuade cardiac damage, arrhythmias, severe coronary syndrome and venous thromboembolic complications. Patients of COVID-19 having already cardiovascular problems showed severe symptoms of this disease and have greater chance of death. This review article especially pays attention on cardiovascular symptoms of COVID-19 and its enhanced effect on patients with already existing cardiovascular diseases.

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INTRODUCTION

COVID-19 epidemic, is an infectious disease and an ongoing global issue. It is severe acute respiratory syndrome caused by coronavirus 2 and is also known as SARS-CoV-2. The infectious issue was initiated in December 2019 in Wuhan, Hubei Province China (Adao and Guzik, 2020; Zheng *et al*., 2020). It is caused by a novel single stranded RNA enveloped beta-coronavirus (Lu *et al*., 2020). Clerkin *et al*. (2020) stated about this innovative RNA virus as the seventh known human coronavirus which is very different from already known viruses such as 229E, OC43, NL63, and HKU1. All these coronaviruses are usually involved in the spread of mild respiratory diseases or common cold. However, this coronavirus is similar to the zoonotic viruses such as severe respiratory disorder coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome (MERS). SARS-CoV-2 must have originated from bats, similar to several other coronaviruses which originate from animals. The virus has 89-96 % and 79.6% nucleotide identity similar to bat corona viruses and SARS viruses respectively (Clerkin *et al*., 2020; Nishiga *et al*., 2020). Moreover, this coronavirus progressed from bats to an intermediate host Malayan pangolin which shares 91% of nucleotide patterns and then to hominids (Fisher and Heymann, 2020).

According to a report by the World Health Organization dated August 12, 2020, approximately 20,542,666 confirmed coronavirus cases were reported in 213 countries worldwide, resulting in 746,335 deaths. The rest of 13,460,635 people have recovered. From the day one the virus is deadly affecting lungs with acute respiratory depression (https://hms.harvard.edu/news/coronavirus-heart). However, heart damage has recently emerged as one of the shocking consequences in the potential ailments caused by this virus.

The virus interacts in the organisms at many levels and develops disease in patients especially those who already have heart conditions and causes myocardial injury and dysfunction. The mechanism is well known that the virus requires enzyme ACE2 receptors to enter the cell.

Coronavirus can also cause serious inflammation of the heart, or myocarditis, which prevents the heart from doing its job properly. According to Nishiga *et al*. (2020) infection with COVID-19 has the ability to damage the heart and cause heart failure. A group of 191 sufferers of COVID-19 in Wuhan, China was recorded which showed 8% of the subjects out of 15 patients, had symptoms of heart failure. An elevated level of cardiac troponin (a protein released into the bloodstream by damaged heart tissue) as well as abnormalities in electrocardiograms and heart ultrasound was also noticed (Tersalvi *et al*., 2020; Zhou *et al*., 2020). According to Guzik *et al*. (2020) and Sandoval *et al*. (2020) various symptoms such as cardiac arrhythmias, cardiomyopathy, and cardiac arrest in several patients of COVID-19 were identified. Although, various drugs such as Rakuvirin, Lopinavir and Ritonavir are widely used to treat Covid-19 patients which produced

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serious effects on the cardiovascular system (Table I) (Gori *et al*., 2020).

Table I. Impact of drugs on cardiovascular patients (Gori *et al*., 2020).

Drug	Cardiovascular side effect	Percentage
Ribavirin	Anemia	>10%
	Tachycardia	01–10%
	Myocardial infarction	0.1–1%
	Cardiomyopathy, arrhythmia	<0.1%
Lopinavir	Hypertension	01–10%
Ritonavir	Deep vein thrombosis	0.1–1%
	Ischemic events	0.1–1%
	Atrioventricular (AV) Block	0.1–1%
	Increased concentration of amiodarone, dronedarone	
Chloroquine/ Hydroxychloroquine	Hypotension, ECG changes	0.1–1%
	Cardiomyopathy	<0.1%

MYOCARDIAL INJURY

Acute cardiovascular injury characterized by significant increase in heart troponins, is the most regularly detailed heart variation from the norm in COVID-19. It happens in around 8–12% of all patients. Acute coronary event (reported to be low), cardiovascular breakdown (in one investigation 52% in the individuals died while 12% recovered and were discharged) and arrhythmia 16.7% global; 44.4 in extreme ailment, 8.9% in gentle cases) were reported. A meta-examination of six distributed investigations from China incorporating 1527 patients with COVID-19 announced 16.4% cardio-cerebrovascular ailment (Bansal, 2020). According to one study, effects of new coronavirus are more devastating for heart patients. As in an early single-focus report portraying hospital cases tainted with pneumonia because of SARS-CoV-2, 23% had prior CVD, especially coronary artery disease (CAD) (Ganatra *et al*., 2020).

In one study, SARS-CoV-2-related myocardial infarction in Wuhan was reported in 5 of the 41 primary patients of COVID-19. An increase in levels of the potent troponin I was recorded in four of the five patients with myocardial injury that were admitted to the emergency department. High blood pressure levels were found in cardiac patients which were treated in the ICU. Half of the patients initially went to see a specialist because of the side effects of the heart. Patients reported heart palpitations and shortness of breath in contrast to the manifestations of breathing, for example, fever and cough, but were later found to have COVID-19 (Zheng *et al*., 2020). Severe side effects such as hypertension (58%), coronary disease (25%), and arrhythmia (44%) were noticed in the patients of COVID-19 (Zheng *et al*., 2020).

The negative myocardial effect of COVID-19 is currently shown to be ‘severe heart damage’, which is characterized by high blood pressure levels of bio signals [high-sensitivity troponin I hs–Tn I] up to the ninety-ninth centile limit of the data. COVID-19, which tolerates flu-like indications, quickly declines into respiratory distress, hypotension, and cardiogenic traumas. A primary condition of cardiovascular injury has a direct relation to the myocardial infarction and acute respiratory disorder caused by coronavirus 2 (SARS-CoV-2) (Tavazzi *et al*., 2020).

Cardiac expression of COVID-19 are complex in patients with AMI (acute myocardial infarction), myocarditis causing ST-rise MI (infection of myocardial infarction), stress cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm, or unexplained myocardial injury (Mahmud *et al*., 2020). Myocardial infarction includes severe coronary heart disease, heart failure, myocarditis, hypotension or shock, and sepsis. Severe arrhythmias, including ventricular tachycardia and fibrillation, also occur in patients with high troponin levels (17.3% of patients with high troponin) (Siordia, 2020).

The pandemic COVID-19 may cause heart injury directly or indirectly because of a staggering immune inflammatory reaction and cytokine storm SARS-CoV-2 viral intrusion of cardiomyocytes. However, this has not been demonstrated in pathology. Serious hypoxia from intense respiratory damage brought about by virus brings oxidative pressure and may cause myocardial injury. So, patients with coronary artery disease or cerebrovascular disease had relatively 3.3 higher hazard proportion of having serious ailment. They require ICU care contrasted with those without cardiovascular disease. Moreover, patients with inborn heart disease could be considered at higher risk for complexity from COVID-19 (Tan and Aboulhosn, 2020).

Preliminary reports from China proposed that the mortality rate of COVID-19 was significantly higher in patients with CVD (13.2%) than other diseases. A significantly higher impact of COVID-19 was recorded in cases with the cardiovascular risk factors such as diabetes (9.2%) and high blood pressure (8.4%) in comparison to 1% patients who do not have such comorbidities (Ganatra *et al*., 2020).

Myocardial infarction is one of the key pathogenic effect of COVID-19. Cardiovascular indications are not very different from already reported coronaviruses epidemics. In 2016, a case report kept a patient with MERS-CoV diagnosed with severe voluntary heart failure in myocarditis confirmed by cardiac MRI. Earlier,

in 2009, another team of scientists recommended that communication between the SARS-CoV family and the ACE-2 family intervened in myocardial injury that led to systolic dysfunction and arrhythmias. Similarly, these recent reports have recommended that patients experiencing myocardial injury from SARS-CoV-2 are at greater risk of hospital mortality (Babapoor *et al*., 2020). Cardiac events associated with covid-19 at first glance include myocardial injury, especially in patients with severe infection, myocarditis, and myopericarditis with decreased systolic function, cardiac arrhythmias, heart failure, and acute coronary heart failure. The prevalence of this virus was allied with an unexplained condition in a surveying study from China, which may have increased the risk of venous thromboembolism changes along with pulmonary embolism. Chest discomfort was a sign which alerts physicians to the possibility of covid-19 (Vetter *et al*., 2020). Data from the Chinese National Health Commission showed that 35% of patients who decided to have COVID-19 had high blood pressure and 17% had heart disease. In a study, 138 patients of COVID-19 that admit to a hospital in Wuhan, China, cardiac arrests elevated sensitivity to troponin (hs-cTnI) or new ECG or echocardiographic abnormalities were found in 7.2% of high-speaking patients and in 22% patients who needed ICU care. However, approximately 12% of the patients without known CVD have elevated troponin levels or heart failure during hospitalization (Clerkin *et al*., 2020).

SYMPTOMS OF COVID-19

The most common signs of disease were fever (up to 88.7% of patients at the time of hospitalization) and cough (in 67.8% of patients), followed by headache, exhaustion or difficulty in breath.

The frequent cardiovascular disorders include abnormal muscular contraction of heart muscles (atrial fibrillation, ventricular tachyarrhythmia, and ventricular fibrillation), heart damage [high troponin I (hs-cTnI) levels and creatine kinase (CK) levels], chronic myocarditis, heart failure, pulmonary embolism and prolonged intravascular coagulation (DIC). Cardiac problems related to SARS-CoV-2 may indicate a process of replication and transmission of the virus through the blood or lymphatic system from the respiratory tract (Inciardi *et al*., 2020). Technically, after the degradation of S protein by serine protease, SARS-CoV-2 is attached to the enzyme that converts transmembrane angiotensin 2 (ACE2), enters type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocyte. This can cause myocardial dysfunction, endothelial cell proliferation, microvascular dysfunction, plaque disorder, and myocardial infarction (MI) (Guzik *et al*., 2020).

The infection assaults globally and with high proficiency; however, its most threatening effect is on the old people, particularly those with cardiovascular ailment, for example, diabetes mellitus, hypertension, and coronary heart disease. Old patients with cardiovascular infection and diabetes frequently have left ventricular hypertrophy, diastolic dysfunction, and even heart failure. Observations proposed a high recurrence of cardiovascular events, with patients of cardiac arrhythmias and heart failure (Mehra and Ruschitzka, 2020).

Mehra *et al*. (2020) also reported symptoms of COVID-19 recorded as cardiac arrhythmia, chronic obstructive pulmonary disease, cardiomyopathy, acute coronary syndromes, and heart failure. While, Lodigiani *et al*. (2020) also narrated that patients of COVID-19 which was self-confessed to a University hospital in Milan, Italy showed significant signs of thromboembolic, comprising venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS)/ myocardial infarction (MI). Another effect is also specified to it as Disseminated Intravascular Coagulation (DIC). Driggin *et al*. (2020) reported disease is related to indirect cardiac arrest including severe myocardial injury, myocarditis, arrhythmias, and venous thromboembolism.

One COVID-19 study typically exhibits low-grade respiratory infections, with a large proportion of patients experiencing adverse cardiovascular effects when they begin to develop. These symptoms include stiffness and tightness of the chest. In addition, all these things, SARS-CoV-2 can cause myocardial damage. In various reports, an increase in troponin I (cTnI) with high sensitivity (cTnI) was observed in 10–20% of COVID-19 patients. ACE2 (angiotensin-converting enzyme 2) also regulates vital cardiovascular functions, including the regulation of blood pressure and glycemia. Whether SARS-CoV-2 directly affects the cardiovascular system by focusing on ACE2-expressing cells is yet to be investigated. Other possibilities include the indirect effect of SARS-CoV-2 immune response on myocardium and vessels. The potent COVID-19 induces cytokine storms, which may play a role in the instability of coronary arteries, as previously noted by SARS-CoV (Hulot, 2020).

The cardiovascular system (CVS) seems to have multifaceted interactions with the COVID-19. Studies of myocardial damage in 20-40% of hospital attendees showed thoracic pain, complete heart failure, cardiac arrhythmias, or heart death. In fact, the manifestations of thoracic pain is the most common symptom in some patients. The basic clinical indications appear within 11.5 days [95% assurance period (CI) of 8.2-15.6 days] and include fever, dry cough, exhaustion, loss of taste, and

headache. Other unexplained symptoms are also listed, including nasal congestion, rhinorrhea, sore throat, muscle pain, loss of appetite, and diarrhea. Usually at 6th days colds and coughs usually occur in conjunction, tracked by shortness of breath and severe fatigue, were recorded while latterly, the symptoms are followed by development of painful (and rarely) chronic lung disease. A few patients have reported side effects of CV, for example, heart tremors and chest tightness, instead of respiratory symptoms (Guzik *et al*., 2020). Common COVID-19 cardiac symptoms include left ventricular dysfunction, heart failure, arrhythmias and acute coronary syndromes. Moreover, severe cardiac grievance, left ventricular (LV) paralysis, heart failure, ventricular arrhythmias, ECG changes, increased B-type natriuretic peptide (BNP) and troponin. Troponin elevations are an indication and may indicate myocarditis or myocardial infarction (MI) (Guo *et al*., 2020; Zaman *et al*., 2020).

Liu *et al*. (2020) reported infection of the myocardial tissues can lead to myocarditis, cardiac failure, cardiac arrhythmias, acute coronary syndrome, rapid decay, and sudden death. Moreover, high exposure to COVID-19 in CVD patients results in pericarditis, vasculitis, and cardiac arrhythmias.

SARS-COV-2 AND CVD

1. SARS-CoV-2 is transmitted by binding the extra HIV protein to the human receptor (ACE2) after reactivation of the spike protein by transmembrane protease serine 2. It is very clear that ACE2 are present in the heart, considering the effects of angiotensin II in regions in addition to the high implementation of renin-angiotensin system, for example, high blood pressure, heart failure, and atherosclerosis (Clerkin *et al*., 2020).

2. In addition to the respiratory system, ACE2 is present significantly in the human cardiovascular system, so SARS-CoV-2 can be a reason for the myocardial damage. The mechanisms involved in ACE2 signaling pathology has shown that cellular ACE2 levels decrease in SARS-CoV infection, cytokine storm and myocarditis. However, the mode of myocardial organization and its severity varies in people with the virus. While myocardial injury is evidenced by high cardiac symptoms, for example, troponin-sensitive heart rash has been identified and reported for myocarditis-induced myocarditis, even if the heart attack includes severe arrhythmias is not yet known (Wu *et al*., 2020).

3. Li *et al*. (2020) reported COVID-19 attach to ACE2 (angiotensin-converting enzyme 2) prompts extreme release of Angiotensin II through RAS, which troubles heart and vascular system, by expanding heart loading, ultimately cardio-myocytes hypertrophy and hypertension develops. Patients show symptoms with palpitation, chest tightness, and shortness after exercise etc. When such patients were affirmed or suspected as COVID-19, an unexpected acute myocardial infarction or heart failure will occur rapidly.

PATIENT WITH UNDERLYING CARDIO-VASCULAR AILMENT

COVID-19 patients with pre-existing heart disease are included in the most prominent recurrence in the intensive care unit, and they certainly suffer the highest mortality rate. A separate study noted cardiovascular intake of COVID-19, instead of respiratory, for example, severe pericarditis and ventricular dysfunction. In another study with the COVID-19 patients showed that 25% had heart disease, 44% had arrhythmia, and 58% had high blood pressure. It was also noticed that prevailing virus has higher impacts on patients with already cardiac issues and higher mortality rate were recorded than those who were without this disease (51.2% compared to 4.5%, each). The virus infects cells containing enzyme 2 (ACE2) receptors that can promote pneumonia, severe myocardial injury, and chronic cardiovascular infection (Aghagoli *et al*., 2020). Chung *et al*. (2020) also reported that patients with pre-cardiovascular disease (CVD) are at higher risk of developing coronavirus 2019 (COVID-19) and have more severe side effects after infection. COVID-19 cardiac complications include my pericarditis, fatal arrhythmias, and biventricular heart failure. Patients with a severe case of COVID-19 often experience severe myocardial injury, as evidenced by elevated troponin levels, which are undoubtedly linked to clinical decline and high death (Gupta *et al*., 2020). In cases of myocardial infarction, the expectation is worse for those with a previous history of CVD. The mortality rate of coronary heart disease (10.5%) is higher than in patients with chronic respiratory disease (6.3%). Reports have suggested that COVID-19 could cause severe heart failure. Severe myocardial injury has been shown in 5 out of the first 41 people diagnosed with the virus in Wuhan, who often exhibited high levels of troponin I (Adão and Guzik, 2020). Guo *et al*. (2020) reported in a study that approximately 66 (35.3%) had CVD including high blood pressure, heart disease, and cardiomyopathy, and 52 (27.8%) showed myocardial injury as indicated by higher TnT levels. (Troponin T) among 187 patients confirmed COVID-19. Patients with chronic coronary artery disease and those with risk factors for atherosclerotic heart disease have a higher risk of developing acute coronary syndrome during acute inflammation. It is predicted that patients with pre-

cardiovascular disease, more common in adults, may be at greater risk of serious side effects and death during severe and aggressive inflammatory responses to COVID-19 than in healthy and young people. Patients at risk for myocardial injury were significantly older and more likely to have high blood pressure, cardiovascular disease, heart failure, and diabetes than those with normal TnI or TnT (troponin T) levels (Bonow *et al*., 2020).

Analysis A total of 1558 patients with COVID-19 in 6 studies were enrolled in the final meta-analysis. High blood pressure, chronic obstructive pulmonary disease, cardiovascular disease were independent risk factors associated with COVID-19 patients (Wang *et al*., 2020).

A 53-year-old white woman presented the emergency department with great fatigue. She developed a fever and a dry cough at last week. She was febrile yet hypotensive; electrocardiography showed an increase in ST, and elevated high levels of troponin T and NT-pro BNP. Findings in chest radiography were common. There was no evidence of coronary infection in coronary angiography. As a result of the COVID-19 outbreak, a nasopharyngeal swab was developed, with a positive effect on SARS-CoV-2 in real-time reverse transcriptase - polymerase chain reaction test. Cardiac magnetic resonance imaging showed increased wall tension with biventricular hypo-kinesis, especially in the apical parts, and severe ventricular dysfunction (a fraction of ventricular ejection fraction of 35%). Short reversal of tau inversion and T2 map sequence showed marked edema of biventricular myocardial interstitial edema, and there was also an improved over time distribution of gadolinium including the entire biventricular wall. There were circular rays that were often noticeable near the right heart chamber. These findings were all strongly correlated with acute myo-pericarditis with systolic dysfunction, confirmed in magnetic resonance imaging, a week after the onset of fever and dry cough due to COVID-19. The patient did not show any respiratory involvement during the course of treatment. The report suggested that cardiovascular complications were linked to COVID-19, with no signs and symptoms of internal pneumonia (Inciardi *et al*., 2020).

The first human infection with a new type of corona virus, SARS-CoV, was reported in 2002 when it was discovered that, at least in rabbits, coronavirus could develop cardiomyopathy which led to a decrease in cardiovascular function and a deterioration of systolic function, causing further damage and extended cardiomyopathies. Now hypotension, cardiac arrhythmias, and sudden cardiac death (SCD) have been shown as unimaginable manifestations of SARS-CoV -2 also (Kochi *et al*., 2020). In a cohort of 121 patients, the cohort showed that sinus tachycardia was the most common form of SARS-CoV with a frequency of 72%. Tenacious tachycardia means that the duration was 12.7 days with a pulse rate of 117 beats / min (range: 102-150 beats / min) and tachycardia persists in 40% of patients within 30 days after discharge of the clinic. Meta-regression analysis for cardiovascular disease demonstrated that the association between cardiovascular ailment and composite helpless result was not affected by gender, age, hypertension, cerebrovascular infections, diabetes, and respiratory comorbidities (Pranata *et al*., 2020).

An analysis of 4189 affirmed COVID-19 patients from 28 investigations was carried out. More serious COVID-19 disease was related with higher mean troponin, with a comparable pattern for creatine kinase–MB, myoglobin, and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Acute cardiovascular injury was more successive in those with serious, instead of mild infection. Meta regression proposed that heart injury biomarker differences of severity are identified with a history of hypertension. COVID19-related heart injury is linked with higher mortality. hsTnI and NT-proBNP levels are increased during the course of hospitalization in non-survivors (Li *et al*., 2020).

CONCLUSION

Covid 19 is a global pandemic in these days that is caused by SARS COV-19 which infects the host cell through ACE2 and causes severe heart diseases like myocardial injury, cardiac arrhythmias and acute coronary syndrome. SARS COV increases the troponin I in the heart which changes the functions of the heart. Patients with preexisting cardiovascular disease are at high risk of coronavirus. Drugs like ribavirin, chloroquine etc. used in the treatment of Covid 19 have a negative impact on heart. A report suggested that mortality rate was higher among patients with CVD.

Statement of conflict of interest

The authors have declared no conflict of interest.

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