



**COVID-19 PANDEMIC: A REVIEW OF CARDIOVASCULAR MANIFESTATION,
COMPLICATION AND FUTURE PROGNOSIS**

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Article Received on 19/08/2020

Article Revised on 09/09/2020

Article Accepted on 29/09/2020

ABSTRACT

The pandemic of the coronavirus disease-19 (COVID-19), the causative agent of the severe acute respiratory syndrome-2 (SARS-CoV-2), has become a public health emergency of the international concern. The majority of the population is exhibiting signs and symptoms similar to the flu and common cold. Despite that, alveolar damage result in progressive lung failure has also been reported. Although COVID-19 has been reported principally to affect the respiratory system, other system's involvement has also been reported. Cardiovascular involvement has also been underlined in the literature. Cardiovascular involvement in SARS-COV-2 usually corresponds to three situations: (a) cardiac manifestation of the acute coronary syndrome, (b) cardiovascular manifestations of COVID-19 in myocardial injury, myocarditis, arrhythmia, and cardiac arrest (c) cardiac manifestation in patients with comorbidities. The actual disease pathogenesis is unknown; however, direct viral invasion to cardiomyocyte, inflammation of cardiomyocyte due to cytokine and inflammatory markers, activation of the complement system, and lung injury from the virus causing hypoxia leading to oxidative stress, increased oxygen demand, and myocyte injury. Patients with cardiac involvement usually experience a wide range of signs and symptoms such as dyspnea, chest pain, nausea, vomiting, diaphoresis, hypercapnia, tachypnea, and elevation in cardiac biomarkers. The pandemic of SARS-CoV-2 has become a unique challenge for the cardiologist. Various renal manifestations have been observed and reported in many cases, and even renal features may precede the classical respiratory signs and symptoms. In this review, we have summarized the information from published literature including, case reports and open-source data sets, to describe the spectrum of cardiovascular manifestation and complication observed in COVID-19 cases.

KEYWORDS: COVID-19, SARS-CoV-2, cardiovascular, acute respiratory distress, cardiac arrest, complication, pandemic.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), the causative agent of COVID-19 (coronavirus disease-2019), first originated from Wuhan, China, during late December of 2019. It started as an outbreak which led to an epidemic with 44,672

confirmed cases in China by February 14, 2020, with a 2.3% reported mortality rate, which was comparatively lower than the previously known epidemics caused by human coronaviruses (Severe Acute Respiratory Syndrome Coronavirus [SARS-CoV] and the Middle East Respiratory Syndrome Coronavirus [MERS-CoV])

in 2003 and 2012 respectively.^[1,2] It rapidly spread outside of China to the rest of the world, mainly through human-to-human transmission by respiratory droplets or possibly through the fecal-oral route. Consequently, the World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020.^[3] Currently, with the disease spread to 216 countries, there are over 27,769,074 reported confirmed cases worldwide, including over 19,851,252 deaths as of September 09, 2020.^[4] The infection presents most commonly as fever, dry cough, shortness of breath, sore throat, and diarrhea with severe respiratory involvement in patients with advanced age (over age 80). The overall case fatality rate in this age group is about 14.3%.^[5] The severity of this disease is characterized by severe pneumonia, respiratory failure requiring mechanical support, sepsis, myocardial injury, multi-organ failure, and mortality increases in patients having underlying comorbidities such as cardiovascular disease, diabetes, chronic kidney disease, and chronic respiratory disease.^[6,7] However, some patients may have very mild symptoms or act as asymptomatic carriers suggesting that the actual number of cases may be much higher than reported.^[2] Given the rapid spread of the virus, researchers across multiple nations have dedicated themselves to understand the virus, disease pathophysiology better, and develop effective drugs and preventive vaccines.

Even though, Although COVID-19 has been reported principally to affect the respiratory system, cardiovascular involvement has also been underlined in the published literature, raising the concerns about cardiac invasion by COVID-19. The amount of literature on cardiac involvement by COVID-19 is small. However, we believe that a structured summary of existing data at this point would be requisite for cardiologist. Being well informed about the cardiac presentation would not only provide support to them have a high index of clinical doubts but also take obligatory precautions. In this paper, we have summarized the information from published literature, including case reports and open-source data sets, to describe the spectrum of cardiovascular manifestation and complications observed in COVID-19 cases.

MATERIAL AND METHODS

We systematically reviewed the literature on COVID-19 and its relevance to our cardiology practice. A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words) including 'COVID-19'/'SARS-CoV-2', and "cardiology/cardiovascular". Pubmed, EMBASE, and Cochrane Library were searched up to 20th July 2020. A limit of after 2019 was imposed since COVID-19 was first reported in late 2019. Additional articles were sought from the reference lists of the included studies. All articles identified from the literature search were screened by two independent reviewers. We included studies on COVID-19 in adult patients. Case reports, case series, observational studies, non-randomized

studies, and randomized trials that were published in English were included in this review. Conferences abstracts, letters to editors, commentaries, and editorials were also included. Studies related to obstetrics and gynecology were excluded.

For eligible studies, study information including first authors, site of study, inclusion and exclusion criteria, sample size, age, and sex were recorded. A standardized form for data entry has been devised to focus on the following areas: (1) cardiovascular manifestations of COVID-19; (2) special considerations in cardiovascular conditions. Relevant data were analyzed and summarized

Review

Mechanism of cardiovascular invasion and symptomology

The genome of the SARS-CoV-2 consists of single-stranded positive-sense RNA encapsulated within a membrane envelope, which has glycoprotein spikes giving coronaviruses their crown-like appearance.^[7] of the four classes of coronaviruses (alpha, beta, gamma, and delta), SARS-CoV, MERS-CoV, and COVID-19 causative SARS-CoV-2, are included in the class beta. While SARS-CoV, MERS-CoV, and SARS-CoV-2, all attack the lower respiratory tract, SARS-CoV-2 additionally also affects the heart, gastrointestinal system, liver, kidney, and the central nervous system eventually leading to multi-organ failure.^[8,9] Glycosylated spike (S) protein, which is one of the structural proteins encoded by the coronavirus genome, is a major inducer of host immune response. This protein binds to angiotensin-converting enzyme 2 (ACE2) receptor protein located on the host cell surface membrane and mediates the host cell invasion.^[9,10] ACE2 (entry receptor for SARS-CoV) was particularly confirmed in COVID-19 infection regardless of mutations at key receptor-binding domains. Inhuman transmission and pathogenesis of COVID-19 are based on the interactions, involving virus binding, receptor recognition, cleavage of protease, and membrane fusion.

Lung involvement is the primary target for SARS-CoV-2, however, cardiovascular involvement may get involved in several ways. Direct myocardial injury is due to the expression of ACE2 receptors. ACE2 plays a crucial role in the neuro-humoral regulation of the cardiovascular system in healthy individuals and in various disease conditions also. The binding and incorporation of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signaling pathways, leading to acute myocardial, myocarditis, and lung injury.^[11,12] The severe form of COVID-19 cause systemic inflammation throughout the body which results in cytokine storm and acute inflammatory response, leading to injury to multiple organs resulting in multi-organ failure. Various studies have reported a high level of circulating pro-inflammatory cytokines in patients, resulting in myocardial infarction and cardiovascular complications.

One of the main reasons associated with cardiovascular injury is an increased metabolic demand of cardiovascular tissues. Severe systemic infection coupled with hypoxia because of acute respiratory distress can disturb the myocardial oxygen demand resulting in myocardial injury and associated complications. Systemic inflammation also causes plaque rupture and coronary vascular thrombosis. Increased shear stress because of increased coronary blood flow can augment plaque rupture leading to acute myocardial infarction and associated complications. The pro-thrombotic state created by systemic inflammation further increases the risk of cardiovascular injury. Severe systemic illness in COVID-19 can cause electrolyte imbalance especially hypokalemia leading to arrhythmia in patients with underlying cardiac disorders due to the activation of the renin-angiotensin system.^[13] Moreover, many antiviral drugs, corticosteroids, and other therapeutics aimed at treating SARS-CoV-2 may also have harmful effects on the cardiovascular system.

Acute coronary syndrome symptomology

Several studies have reported the manifestation of the acute coronary syndrome in many studies. In a recent study, a small proportion of patients with COVID-19 presented with acute chest pain on admission to the hospital however, the features of the chest pain were not reported in detail.^[14] In a case series, involving eighteen patients with COVID-19 and ST-segment elevation, which is suggestive of potential acute myocardial infarction, five out of six patients with myocardial infarction underwent percutaneous coronary intervention.^[15] Similarly, in another study from Italy involving 28 patients with COVID-19 and ST-segment elevation myocardial infarction, evaluation by coronary angiography revealed that seventeen patients had findings of a culprit lesion that needed for revascularization.^[16] The most important thing was that ST-segment elevation MI was the first clinical manifestation of SARS-CoV-2 in the 24 hours of these patients at the time of coronary angiography. These findings indicate that COVID-19 can cause acute coronary syndrome even in the absence of substantial systemic inflammation and cytokine storm. However, the prevalence of acute coronary syndrome in patients with COVID-19 is still unknown. Because of overwhelming health-care facilities during the COVID-19 pandemic, the number of patients of acute myocardial infarction diagnosed with COVID-19 might be underestimated in many studies. The exact mechanism of COVID-19-induced acute coronary syndrome might involve the rupture of a plaque, coronary spasm, or micro-thrombi in widespread circulation, owing to diffuse inflammation.^[17]

Myocarditis and acute myocardial injury

Acute myocardial injury and myocarditis, as demonstrated by raised levels of cardiac biomarkers or the abnormalities on ECG, were reported in 7–20% of patients with COVID-19 in many studies.^[18] In the

preliminary report of 41 patients with COVID-19, five patients had myocardial injury associated with elevated levels of high-sensitivity cardiac troponin I (>28 pg/ml), and four of these five patients were admitted to intensive care unit. In a recent study of 416 patients with COVID-19, 20% had the manifestation of cardiac injury, which was associated with a 5-fold increase in the need for invasive mechanical ventilation and an 11-fold increase in mortality. Of note, the cardiovascular injury was reported to be an independent risk factor for in-hospital mortality.^[19]

Apart from that, many case reports have reported typical signs of myocarditis in patients with COVID-19. A woman aged 53 years with myocardial injury, as demonstrated by high levels of cardiac biomarkers and diffuse ST-segment elevation on ECG, had diffuse and generalized biventricular hypo-kinesis on cardiac MRI, especially in the apical segments, in addition to severe LV dysfunction (LVEF = 35%).^[20] MRI data also revealed marked biventricular interstitial edema, clinical pictures that are consistent with acute myocarditis. Furthermore, in a man aged 37 years with chest pain and ST-segment elevation, echocardiography reported an enlarged heart (LV diastolic dimension = 58 mm) and LV dysfunction (LVEF = 27%).^[21] An autopsy of a patient with COVID-19 and ARDS who died of a sudden cardiac arrest revealed no evidence of myocardial structural involvement, suggesting that COVID-19 did not directly damage the heart.^[22] Apart from that, another case report reported a patient with low-grade myocardial inflammation and myocardial localization of coronavirus particles, as measured by endo-myocardial biopsy, reporting that SARS-CoV-2 may infect the heart muscle directly. However, whether these patients had myocarditis or whether the findings were the result of systemic inflammation remains unclear. It can be an inference that these findings indicate that myocardial injury, myocarditis, and acute coronary syndrome are not the common manifestation of COVID-19, but also a risk factor for poor prognosis.

Patients with pre-existing cardiovascular disease

COVID-19 in patients with pre-existing cardiovascular disease has also been reported in the literature. Wu *et al.* reported in a follow-up survey of 25 patients who recovered from COVID-19 infection that 68% had hyperlipidemia, 44% had cardiovascular system abnormalities, and 60% had diabetes.^[23] In these patients, the serum level of free fatty acids, lysophosphatidylcholine, lysophosphatidylethanolamine, and phosphatidylglycerol were markedly increased vs individuals without a history of COVID-19 infection. One of the most significant metabolic abnormalities was the comprehensive increase of phosphatidylinositol level in recovered SARS individuals, which accorded with the effect of methylprednisolone administration explored further in the steroid-treated non-COVID patients with critical pneumonia. The authors reported that the high-dose of

methylprednisolone might initiate long-term systemic injury associated with serum metabolic abnormalities. However, the exact mechanisms by which COVID-19 infection leads to glucose and lipid disorders are still uncertain. [According to the Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Version 6), old patients with comorbidities such as hypertension, coronary heart disease, or diabetes have a higher chance to be infected with SARS-CoV-2. Therefore, in SARS-CoV-2 patients, underlying cardiovascular disease can worsen pneumonia and increase the severity of signs and symptoms. When infected with COVID-19, cardiovascular insufficiency is more likely to establish, in these patients. For patients with cardiovascular abnormalities who have underlying heart disease, COVID-19 might act as a precipitating factor to aggravate the condition, leading to death. However, it has not been reported any causative role of such co-morbidities to COVID-19 infection.

Klok *et al.* evaluated the incidence of the outcome of venous thromboembolism (VTE) and arterial thrombotic as complications of COVID-19, have also been reported in the literature. They suggested that the composite outcome consisted of acute pulmonary embolism (PE), deep-vein thrombosis (DVT), ischemic stroke, myocardial infarction, or systemic arterial embolism.^[24]

Heart failure in COVID-19 Patients

Among 799 patients in the early stages of COVID-19, heart failure was one of the most commonly reported complications, with an observed incidence of 24% in all patients and 49% in patients who died. Increased levels of amino-terminal pro-B-type natriuretic peptide were reported in 49% of all patients.^[25] Furthermore, in a study of 191 patients, heart failure was reported in 23% of all patients and in 52% of patients who died.^[26]

Most of the COVID-19 patients are likely to be older and to have pre-existing comorbidities such as coronary artery disease, hypertension, and diabetes. Heart failure in these patients might be the result of an exacerbation of these pre-existing conditions, whether already diagnosed or unknown or the uncovering of subclinical cardiac dysfunction. In particular, elderly patients with reduced diastolic function might develop heart failure with preserved EF during COVID-19, which can be triggered by high fever, tachycardia, excessive hydration, and impaired renal function.^[27] COVID-19 primarily causes lung symptoms and viral pneumonia, the pulmonary edema that is reported in individuals, which is commonly followed by ARDS, which ultimately leads to heart failure.

Arrhythmias and sudden cardiac arrest

Arrhythmias and sudden cardiac arrest are the least reported manifestations of COVID-19. Palpitations have been identified to be the main presenting symptom of COVID-19 patients.^[28] In a study of 138 patients with COVID-19, the presence of cardiac arrhythmia was

identified in 17% of all patients, however, the specific types of arrhythmia were not reported. Similarly, in another study in involving 187 patients hospitalized with COVID-19, those with high levels of troponin T were most likely to experience malignant arrhythmias, such as ventricular tachycardia and fibrillation, as compared to those with normal levels of troponin T (12% versus 5%).^[29] In-hospital and out-of-hospital sudden cardiac arrests have also been underlined in individuals with COVID-19. However, the exact mechanism of COVID-19 to cardiac arrhythmias remains uncertain. Arrhythmias, such as atrial and ventricular tachycardia and fibrillation, can also be triggered by myocardial injury or other causes of systemic inflammation. Furthermore, patients with advanced COVID-19 are managed with antiviral therapeutics and antibiotics that are recognized to induce life-threatening arrhythmias in some patients.^[30]

Future consideration

The management principles for individuals with COVID-19 who develop cardiovascular complications or who have pre-existing cardiovascular disease are usually the same as for any other patient without COVID-19. However, there are a few important points that need consideration. It is our primary responsibility to protect ourselves from being infected while handling these patients. We must observe the necessary precautions and measures at all times. Satisfactory protocols for rapid diagnosis, isolation, and management of COVID-19 with cardiovascular complications should be developed and well-rehearsed. Rapid triaging and efforts should be made to reduce delays in care. Unwarranted diagnostic tests should be avoided. The American Society of Heart Association has issued an advisory regarding the COVID-19 induced cardiovascular patients.^[31] Safety concerns of ACE inhibitors and angiotensin receptor blockers must be identified. Several leading professional societies have strongly indicated to not discontinue clinically-indicated ACEi/ARB therapeutics in the event the patient develops COVID-19 due to favorable effects.

CONCLUSIONS

The pandemic of COVID-19 presents for a cardiologist some exceptional challenges. We perceive that SARS-CoV-2 may have various renal manifestations, and in many cases, the cardiovascular signs and symptoms may precede typical respiratory symptoms. Holistic knowledge of the spectrum of the cardiovascular consequences of COVID-19 is crucial to get a hold on the spread of the virus. The most vital clinical information which we meet is that diarrhea and abdominal pain may be a presenting feature of COVID-19. Therefore, a high catalog of suspicion for such patients will be important to prevent or, at least, minimum exposure to health care providers and other patients. With the gradual settling of the outbreak, it can be predicted that several post-infectious cardiovascular complications including acute coronary syndrome,

myocardial infarction, arrhythmia, and cardiac arrest will surface up. The proper caution has to be practiced while treating and managing patients with cardiovascular comorbidities, particularly those patients on coronary artery bypass graft and myocardiaopathies needing validating therapy since framed guidelines are lacking at this point. The above review of the cardiovascular manifestations of COVID-19 will help the cardiologist have a basic preparation, which is of extreme importance to prevent infections.

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