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REVIEW ON IMPACT OF COVID-19 ON CARDIOVASCULAR DISEASES

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Abstract:

Coronavirus disease 2019 (COVID-19), caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic that has affected the lives of billions of individuals. Many patients with COVID-19 experience acute myocardial injury, as evident by an increase in cardiac troponin levels. A significant proportion of hospitalized patients, particularly those with severe illness developed heart failure (23%). Potential drug–disease interactions affecting patients with COVID-19 and comorbid cardiovascular diseases are also becoming a serious concern. In this Review, we summarize Coronavirus-2 (SARS-CoV-2), Pre-existing Cardiovascular Disease, and Outcomes in Patients with Cardiovascular Disease, Acute Cardiovascular Injury, Mechanism of Cardiovascular Injury and Management Consideration for Specific Clinical Cardiovascular Scenarios in Patients with Suspected or Confirmed COVID-19.

Key words: *COVID-19, Cardiovascular Disease, Management, Outcomes, Review*

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INTRODUCTION:

The emergence of novel coronavirus, officially known as severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2), has presented an unprecedented challenge for the healthcare community across the world. High infectivity, ability to get transmitted even during asymptomatic phase and relatively low virulence has resulted in rapid transmission of this virus beyond geographic regions, leading to a pandemic. The first case of this disease, known as coronavirus disease 2019 (COVID-2019), occurred on December 8, 2019 in the Hubei province of China [1]. Since then, within a short span of just over 3 months, the infection has spread to 177 countries/area/territories across the world, with 266073 confirmed cases and 11184 deaths (World Health Organization statistics as on March 21, 2020) [2] .

Respiratory involvement, presenting as mild flulike illness to potentially lethal acute respiratory distress syndrome or fulminant pneumonia, is the dominant clinical manifestation of COVID-19. However, much like any other respiratory tract infection, preexisting cardiovascular disease (CVD) and CV risk factors enhance vulnerability to COVID-19. Further, COVID-19 can worsen underlying CVD and even precipitate de novo cardiac complications.

Search methods:

A literature search was done using PubMed and Google search engines for original and review articles, advisories from professional societies, and expert commentaries published since the

Table 1 Cardiovascular complications in corona virus disease 2019.

Manifestation	Incidence	Remarks
Acute cardiac injury* (most commonly defined as elevation of cardiac troponin 1 above 99th percentile upper reference limit)	8-12% on average [3]	1.Most commonly reported cardiovascular abnormality 2.Can result from any of the following mechanisms-3.Direct myocardial injury 4.Systemic inflammation 5.Myocardial oxygen demand supply mismatch 6.Acute coronary event 7.Iatrogenic 8.Strong adverse prognostic value
Acute coronary event	Not reported, but appears to be low	Potential mechanisms- 1.Plaque rupture due to inflammation/increased shear stress 2.Aggravation of pre-existing coronary artery disease
Left ventricular systolic dysfunction	Not reported	Any of the causes of myocardial dysfunction mentioned above can lead to acute left ventricular systolic dysfunction
Heart failure	Reported in one study- 52% in those who died, 12% in those who recovered and were discharged [4]	1.Any of the causes of myocardial dysfunction mentioned above can lead to acute heart failure 2.Increased metabolic demand of a systemic disease can cause acute decompensation of pre-existing stable heart failure
Arrhythmia	16.7% overall; 44.4 in severe illness, 8.9% in mild cases [5]	Both tachyarrhythmia and bradyarrhythmia can occur but exact nature not described
Potential long-term consequences	Too early to assess	Too early to ascertain for coronavirus disease 2019. However, patients recovering from a similar earlier illness- Severe Acute Respiratory Syndrome- continued to have long-term abnormalities of lipid and glucose metabolism and of cardiovascular homeostasis [6]

Pre-existing Cardiovascular Disease:
In an early single-center report from China describing hospitalized patients infected with pneumonia due to SARS-CoV-2, 40% had pre-existing CVD, particularly coronary artery disease (CAD) and cerebrovascular disease (4). However, the following larger cohort from China describe a lower overall rate of affected patients with underlying CAD (8%). Beyond preexisting CVD, consistent data have described a high prevalence of SAR-CoV-2 infection among elderly, and with concomitant CV comorbidities, particularly hypertension (30%) and diabetes (19%) [8].While a higher prevalence of CVD, diabetes, and hypertension is reported in patients with severe COVID-19, the impact of these comorbid conditions after adjusting for age and obesity remains unknown.

Outcomes in Patients with Cardiovascular Disease:
Early reports from China show that the COVID-19 mortality rate among hospitalized patients was highest among elderly, and in patients with CVD (13.2%) compared to other comorbidities, and was disproportionately higher for patients with CV risk factors such as diabetes (9.2%) and hypertension (8.4%) compared to approximately 1% for patients without these comorbidities.

Acute Cardiovascular Injury:
Many patients with COVID-19 experience acute myocardial injury, as evident by an increase in cardiac troponin levels. A significant proportion of hospitalized patients, particularly those with severe illness developed heart failure (23%) [7].

Moreover, troponin levels were significantly higher in patients admitted to the ICU and in non-survivors, suggesting that CV complications might contribute to the severity of illness and adverse outcomes. Myocarditis, arrhythmias, and cardiac arrest have also been reported [7].

Mechanism of Cardiovascular Injury:
The exact mechanisms of COVID-19 associated CV injury are not well understood; however, several potential mechanisms include[9]:

i. Direct toxicity through the viral invasion of cardiac myocytes (i.e., myocarditis)
ii. ACE-2 receptor-mediated CV (cardiac and endothelial) injury
iii. Microvascular dysfunction and thrombosis
iv. Cytokine release syndrome (mainly IL-6 mediated)
v. Stress cardiomyopathy due to the imbalance in myocardial supply and demand

Long-term Cardiovascular Effects:
While we do not yet understand the long-term CV impact of SARS-CoV-2 infection, a similar pathogen, SARS-CoV has been associated with dysregulation of lipid and glucose metabolism in long-term survivors. Given the structural similarities between these two pathogens, SARS-CoV-2 may also cause chronic damage to the CV system [7].

Management Consideration for Specific Clinical Cardiovascular Scenarios in Patients with Suspected or Confirmed COVID-19
1. COVID-19 associated myocardial injury:
Approximately 20-30% patients with COVID-19 experienced de novo myocardial injury defined as elevated cardiac troponin with or without cardiomyopathy. While the understanding of this entity is limited and is evolving, typically, the rise in troponin is reported late in the course (4 days after onset of the symptoms/presentation), and many do not have any typical CV symptoms. Elevated troponin is associated with worse outcomes, including the need for admission in intensive care unit (ICU) and increased mortality [7].

The management strategy for patients with COVID-19 associated myocardial injury is not well defined and is largely targeted towards supportive care as well as management of the infection itself .

Diagnostic Recommendations:

a. For patients without any significant CV symptoms and low-level troponin release (e.g. Troponin <2 times upper limit of normal [ULN]), in the absence of hemodynamic instability, we do not recommend routine assessment of left ventricular function, and therefore would not routinely recommend echocardiography during acute COVID-19. This will reduce exposure to HCW as echocardiography is unlikely to change management significantly in these patients. However, this strategy may need to be re-evaluated on a case-by-case basis.
b. For patients with hemodynamic or electrical instability, more than mild troponin elevation or heart failure, further CV testing, including bedside echocardiography or a point of care ultrasound (POCUS), should be considered, based on expertise (8). If the patient with suspected or confirmed COVID-19 has any specific CV symptoms, ECG abnormalities, arrhythmia/heart block, and elevated troponin, CAD and myocarditis should be considered. Although cardiac MRI is considered the gold

standard non-invasive test for the diagnosis of myocarditis, in patients with COVID-19 and suspected myocarditis, the risk of exposure to HCW and other patients should be weighed carefully. If needed, abbreviated imaging tailored to the specific clinical question should be considered. The role of endomyocardial biopsy in this situation is unclear and may be considered if there is a suspicion for an alternative etiology.

Treatment Recommendations:
While there is no specific proven treatment for COVID-19 associated myocardial injury, current therapy is based on reducing viral replication and modulating the host inflammatory response. The choice of therapy should be guided by the severity of illness and hemodynamic compromise.

a. Avoid Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):
NSAIDs are often used in the management of myopericarditis. However, there is a theoretical concern that they may increase ACE-2 levels[11]. Additionally, NSAIDs may also increase the risk of acute kidney injury (AKI). Hence, we recommend avoiding NSAIDs in any patients with suspected or confirmed COVID-19.

b. Experimental anti-viral therapy:
Several anti-viral therapies -are under investigation. Early experience with hydroxychloroquine, with or without azithromycin from France and China in COVID-19 patients with mild symptoms, was promising [12], but a subsequent larger study in patients with severe COVID-19 has not shown any significant clinical benefits [13]. Similarly, a recent large scale multinational registry as well as meta-analysis did not demonstrate any clinical benefit of HCQ [14]. Furthermore, the combination of hydroxychloroquine and azithromycin may cause QT prolongation and life-threatening arrhythmias and should only be used with caution and continuous telemetry monitoring [15]

c. Anti-inflammatory therapies:
While corticosteroids are typically avoided in the treatment of COVID-19, due to the concern for prolonging viral illness, in later stages of inflammation that are typically associated with excessive cytokine release leading to hemodynamic instability and end-organ damage, corticosteroid administration may be considered after a multidisciplinary discussion. While the use of corticosteroids have been efficacious in treating myocarditis from immune checkpoint inhibitors or giant cell myocarditis [16], its use in COIVD-19 related myocarditis has been limited to case reports .

d. Immunomodulatory therapy:
Intravenous immunoglobulin (IVIg) has been utilized in a limited number of cases with COVID-19 associated myocarditis. Given that IVIg is well-tolerated, its potential efficacy in improving passive immunity and modulating inflammation, it might be considered in severely ill patients, at the early stage of clinical deterioration of patients with COVID-19, especially if anti-IL-6 agent is not available.

Convalescent plasma from patients who have recovered from SARS-CoV-2 infection is also being studied as a potential therapy for severely ill COVID-19 patients [18]. However, its specific utility in patients with COVID-19 associated CV injury and feasibility of the therapy is unknown at this time.

2. Acute coronary syndrome (ACS):
There have been reports of ACS in patients with COVID-19; however, the incidence and relationship are unclear [19]. The hyperinflammatory response seen with COVID-19 may lead to coronary plaque destabilization and thrombosis. Therefore, it is crucial that we develop a strategy to provide timely and optimal care to patients with ACS, regardless of their COVID status .

i. Non-ST Elevation Myocardial Infarction (NSTEMI) or Unstable Angina (UA):
Caution is recommended in diagnosing ACS, particularly NSTEMI in patients with COVID-19. Mild elevations in troponin could be secondary to multiple etiologies rather than plaque instability. The diagnosis of NSTEMI or UA should be made based on the clinical presentation and ECG changes, in addition to troponin. Once again, we do not recommend routine echocardiography in patients who are hemodynamically stable without clinical heart failure to minimize the exposure to sonographers, however, POCUS might be considered if needed. Medical therapy with anticoagulation, dual antiplatelet therapy, and high-intensity statins are a reasonable first-line strategy for such patients. Beta-blockers should be considered with caution in patients with decompensated heart failure. Coronary CT angiogram with or without fractional flow

ii. ST Elevation Myocardial Infarction (STEMI):
STEMI in patients with suspected or confirmed COVID-19 may represent plaque destabilization due to acute systemic inflammation and endothelial ACE-2 receptor modulation by SARS-CoV-2 [9]or microthrombi formation. Myopericarditis should be

considered in the differential diagnosis, particularly for young patients without any prior CVD or significant risk factors [15].

3. Type II Myocardial Infarction:
Many patients with COVID-19 may experience type II MI given acute stress, hypoxemia, and excessive inflammation secondary to cytokine release (2). It is important to make the distinction between primary ACS and type II MI in COVID-19 patients to minimize any further downstream CV testing and exposure to HCW. Usually, patients with type II MI do not have angina, troponin rises mildly and without ECG changes suggestive of ischemia or with global ischemia pattern. However, sustained chest pain is a commonly reported symptom of acute COVID-19 in patients with or without myocardial necrosis [8]. For patients with suspected Type II MI, it is reasonable to consider conservative management directed towards the treatment of the underlying acute condition. Supportive care, along with anti-viral, anti-inflammatory, and immunomodulatory medications can be considered as described previously on a case-by-case basis.

4. Venous Thromboembolism (VTE) Prophylaxis and Treatment:
COVID-19 associated hypercoagulability has been reported in early clinical and autopsy data. Although the mechanism is not well understood, it is likely multifactorial and influenced by:

i. Systemic inflammatory response due to infection
ii. Venous stasis secondary to critical illness
iii. Direct endothelial damage from viral injury by ACE-2 receptor binding

5. Arrhythmias:
In a case series of 138 patients, arrhythmias, including atrial fibrillation, were reported in 17% of hospitalized patients, with higher rates in critically ill patients (44%) [20]. In another study of 189 hospitalized patients from Wuhan, China, 5.9% were noted to have ventricular arrhythmias [21]. We recommend baseline 12-lead electrocardiogram (ECG) and telemetry monitoring for all hospitalized COVID-19 patients.

In the hemodynamically stable patient with AF without heart failure, rate control and anticoagulation are preferable to an attempt at rhythm control. An echocardiogram should be deferred for 4-6 weeks after recovery. Atrioventricular nodal blocking agents such as beta blockers, calcium channel blockers, or digoxin can be used for rate control. Drug-drug interactions should be considered in patients on anti-viral therapy. For example, hydroxychloroquine may increase the level of beta-blockers as well as digoxin and may result in toxicity [22]. If a patient has cardiomyopathy, heart failure, or hypotension, short-term amiodarone can be considered. Urgent electrical cardioversion should be performed with

6. QT interval monitoring:
Hydroxychloroquine blocks voltage-gated potassium channel (Kv11.1) and can cause drug-induced QT prolongation by prolonging action potential duration [15]. However, clinically significant arrhythmia is mostly seen in the context of either long-term use or in patients with concomitant use of other QT-prolonging medications (e.g., azithromycin), metabolic 16 derangements, renal failure, or in the setting of an acute overdose. While despite this theoretical risk, hydroxychloroquine is relatively well tolerated for other medical conditions, particularly when used for a short period. However, emerging evidence suggests a significantly increased risk of de novo ventricular arrhythmia when used in hospitalized patients with COVID-19 [23].

7. Use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB):
SARS-CoV-2 uses ACE-2 as a co-receptor for cellular entry. [9] It is hypothesized that ACEi and ARB administration leads to up-regulation of ACE-2 expression in the lung and the heart, thus increasing the risk of SARS-CoV-2 infection and severity of COVID-19 [9]. However, data from animal models of SARS-CoV infection have shown improvement in virus induced lung damage with ACEi/ARB treatment. Thus, the role of ACEi/ARB in COVID-19 remains unclear and clinical trials are underway to assess the safety and efficacy of the renin 17 angiotensin-aldosterone system (RAAS) modulators, in patients with COVID-19 . At present, major societies (ESC/AHA/ACC) recommend continuing ACEi or ARB in patients who take these medications chronically . Besides, if a COVID-19 patient develops cardiomyopathy or heart failure, these agents should be administered as per guidelines.

9. Mechanical support for cardiogenic shock and use of Extracorporeal Membrane Oxygenation (ECMO):
The use of percutaneous mechanical circulatory support (MCS) in the setting of cardiogenic shock is generally supported by weak evidence demonstrating a favorable hemodynamic impact. Given the paucity of supportive evidence for MCS devices, the calculus is even more complicated in the setting of an infectious disease with an undefined clinical course

and the risk posed to operators involved in the deployment and management of these devices. Thus far, in the COVID-19 pandemic, there has been very little reported use of MCS devices. Even venovenous ECMO for respiratory failure has been used rarely to support patients with refractory hypoxemia [20]. Despite the lack of clarity, it may still be prudent to offer MCS to select patients (young age, limited comorbid ailments without multi-system organ failure) with cardiogenic shock who are refractory to optimal medical therapy.

10. Cardiac arrest and considerations for resuscitation:

18Patients who are critically ill with COVID-19 are at very high risk of cardiac arrest either with pulseless electrical activity or ventricular arrhythmia [21]. It is crucial to identify patients who are at high-risk for acute decompensation, and goals of care should be discussed early on to avoid any unwarranted resuscitation efforts. Because of the risk of viral aerosolization in the setting of unplanned resuscitation, early intervention with intubation should be considered for patients with impending respiratory failure [15].

Preparation for post-COVID-19 era:

While we are currently focused on how to navigate the medical care during the COVID 19 pandemic, we need to recognize than many non-urgent but required CV testing and procedures are being significantly delayed, which may have a long-term adverse impact. As we try to re-open and normalize, one of the daunting tasks will be to identify high-risk patients, so limited resources can be prioritized to expedite the care of such patients. Although we will be required to ramp up the outpatient visits and CV testing as well as procedures in order to minimize any further delay in care, we need to maintain a high-index of suspicion and precautions to prevent re-surge of the COVID-19. Furthermore, the policies and strategies developed today will serve as the basis for addressing the next similar crisis.

CONCLUSION:

The COVID-19 pandemic has produced devastating effects worldwide with loss of health, life, and livelihoods, particularly in people of color, the underserved, the vulnerable elderly, and those with prior cardiovascular disease. Present Review article give detailed about Coronavirus-2 (SARS-CoV-2), Pre-existing Cardiovascular Disease, and Outcomes in Patients with Cardiovascular Disease, Acute Cardiovascular Injury, Mechanism of Cardiovascular Injury and Management Consideration for Specific Clinical Cardiovascular Scenarios in Patients with Suspected or Confirmed COVID-19.

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