ABSTRACT

Coronavirus disease (COVID-19) is a serious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that continues to grow globally. Incidence of cardiovascular complications has increased during the COVID-19 (Coronavirus disease 2019) pandemic, in regards of population-wide and in patients diagnosed with the disease. Various cardiovascular manifestations have been linked to the viral insult, including among others acute coronary syndromes, myocarditis, acute heart failure, cardiac injury, arrhythmias spontaneous coronary artery dissection, and stress induced cardiomyopathy. Although, the mechanism of heart injury in COVID-19 is not clear yet, several hypothesis and theories to various cardiac manifestation have been described. We performed a narrative review for the current published literature on the different cardiovascular manifestation related to COVID-19 infection.

Keywords
Covid-19, Arrhythmia, SARS-CoV-2, Myocarditis, Cardiac injury, ACS, Takotsubo cardiomyopathy.

Introduction
Coronavirus disease 2019 (COVID-19) is an ongoing pandemic that has affected millions of individuals worldwide. First appeared in Wuhan, China. The World Health Organization officially declared it in March 2020. The clinical manifestations of COVID-19 may range from asymptomatic or mild respiratory symptoms to severe life threatening respiratory and cardiac failure [1]. Myocardial injury is common in patients with COVID-19, accounting for 7%-23% of reported cases in Wuhan, China. [27-29]. Among COVID-related myocardial injury, etiologies vary and might include myocarditis, myocardial infarction, cardiogenic shock, conduction disturbance, and stress-induced cardiomyopathy (takotsubo cardiomyopathy) [26,77]. Furthermore, cardiovascular complications have reported as some of the most significant and life-threatening manifestation, which might herald poor prognosis [1-4]. Some studies have found that myocardial injury with an elevated troponin level may occur in 7–17% of patients hospitalized with COVID-19 and 22–31% of those admitted to the intensive care unit (ICU) [8-11]. Infection affects cardiac relevant biochemical pathways such as the ACE2 signaling pathway, cardiac muscle integrity, fibrinogen pathways, redox homeostasis, induces a break in plaque associated with the stent, and finally, aggravates a myocardial injury and dysfunction [5]. Several case reports of hospitalized patients suggest that COVID-19 prominently affects the cardiovascular system, but the overall impact until this point remains unknown. Furthermore, these CV related manifestations portend greater morbidity and mortality, which requires clinicians to be familiar with the most recent information to provide informed patient care. Thus, the aim of this review is to numerate the variety of cardiovascular manifestation associated with covid-19 infection, which is critically important in the care and the long-term outcome of patients with COVID-19.

Pathogenesis of myocardial injury
SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus. It is similar coronaviruses, which use the ACE 2 (ACE2) protein for ligand binding before entering the cell via receptor-mediated endocytosis [12]. After entering the cells via ACE2 receptors, SARS-CoV-2 down-regulates the ACE2 expression such that the enzyme is unable to exert organ protective
effects [71]. ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) upregulate the number of ACE2 receptors on the surface of myocardial, alveolar and gastrointestinal cells which has raised the concern of ACEI and ARB induced increase in COVID-19 acquisition into the myocardial and alveolar cells [72-74]. Moreover, a recent study of COVID-19 patients, there was cardio myocyte hypertrophy, degeneration and necrosis of cardio myocytes, mild interstitial hyperaemia and oedema along with infiltration of lymphocytes, monocytes and neutrophils but no virus component in the myocardial tissue. While in another autopsy report, there was scattered individual cell myocyte necrosis with lymphocytes adjacent to, but not surrounding, degenerating myocytes, which might represent an early manifestation of a viral myocarditis [69,70]. In addition, several clinical reports on COVID-19 patients reported significantly elevated inflammatory biomarkers in circulation, including interleukin (IL)-2, IL-6, IL-7, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), tumor necrosis factor-α (TNF-α), interferon-γ inducible protein (IP)-10, C-reactive protein (CRP), ferritin and procalcitonin. Although triggered by local infection in the lungs, the increased systemic levels of these inflammatory cytokines activate inflammatory and maladaptive remodeling pathways in multiple organs, including the heart [75,76].

**Myocarditis**

Myocarditis refers to the inflammation of the cardiac muscle due to a variety of infectious and non-infectious diseases [19]. Myocarditis was reported with an incidence of 12.5% in one cohort study, variety of clinical presentations are associated with myocarditis, ranging from mild symptoms such as fatigue, chest pain, and palpitations to life-threatening presentations such as cardiogenic shock or sudden cardiac arrest associated with malignant arrhythmias [20]. The exact pathophysiology of SARS-CoV-2-associated myocarditis remains obscure currently. Depending on host-immune response and the phase of infection, ranging from acute, subacute, or chronic. Proposed mechanisms may include: (1) immune-mediated, (2) autoimmune-mediated, and (3) direct virus-induced cardiovascular injury, in which SARS-CoV-2 may invade cardiac myocytes using their surface ACE2 receptors and may cause direct cellular damage [16,21,22]. Hence, viruses evade the innate immune system; they replicate and create viral proteins that cause direct myocardial damage by inducing cellular apoptosis and necrosis [37]. Although, SARS-CoV-2 likely causes myocarditis in humans through one of the pathways resemble the other viral pathogens [23,24]. Moreover, in other proposed pathophysiology of viral myocarditis is based on activation of interleukin-6 (IL-6) and triggering of a subsequent cytokine storm, combined with direct myocardial injury, Plasma levels of IL-1β, IL-6, IL-8 and TNF-α have been found to be significantly higher in patients with COVID-19 [57]. The clinical and biochemical profiles of non-survivors in patients with COVID-19 with highly elevated ferritin and IL-6 also suggest that cytokine release contribute to mortality [18]. Keeping in mind that the precise incidence of COVID-related myocarditis is still unknown [30].

Although, there is no single laboratory test exists to establish the diagnosis of myocarditis, however, several investigations can aid in the diagnosis. Serum troponin values will be elevated. The electrocardiogram (ECG) can demonstrate a range of findings, in some cases mimicking acute coronary syndrome (ACS). The American Heart Association recommends echocardiography or cardiac magnetic resonance imaging (MRI), while the definitive diagnosis requiring an endomyocardial biopsy. In the absence of a cardiac MRI, contrast-enhanced CT is recommended [31]. Nevertheless, CMR is not indicated in case of hemodynamic is recommended [33]. Transthoracic echocardiography (TTE) is the recommended initial imaging modality of choice to evaluate for COVID-19-associated cardiac complications. Findings might include global left ventricular (LV) or biventricular dysfunction, myocardial edema, LV thrombus, and pericardial effusion, which may be a complication of peri-myocarditis [32]. Endomyocardial biopsy (EMB) is often considered to aid in the definitive diagnosis of myocarditis. Two studies reported the results of endomyocardial biopsies [34,35], both samples revealed active inflammation, and only one found viral particles within the myocardium [34]. While no single treatment strategy has been found efficacious, the Systemic steroids and immunosuppression should be used in cautious; hence, they might exacerbate COVID-19-associated lung injury [36]. the use of the antiviral medications lopinavir-ritonavir was reported in 62.5% of studies, with variable results [36-41]. While the utilization of hydroxychloroquine and human immunoglobulin has been also described in, however, several studies showed there was no evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection [36-41]. Piperacillin-tazobactam [36,38,39], and extracorporeal membrane oxygenation [37-39], each as single therapeutic interventions was described in 37.5% of case reports with controversy results. The use of inotropes and/or vaspressors was reported in 50% of studies [36-38,40]. Heart transplantation would not be an option for patients with COVID-19-associated myocarditis because of their active and ongoing infection [42]. Instability as in severe heart failure, circulatory shock, ventricular arrhythmia, or high-grade AV block, in which cases an EMB.

**Arrhythmias**

Arrhythmia could be the first presentation of COVID-19. Either a new-onset and/or progressive arrhythmia could indicate cardiac involvement. With a prevalence of 7.3 % [43]. In another study of 138 hospitalized COVID-19 patients, arrhythmia was noted in 16.7% of patients and was more common in those patients admitted to the intensive care unit (ICU) in comparison to non-ICU patients (44.4% vs. 6.9%, p<0.001) [46]. While Sinus tachycardia was the most common rhythm disturbance in patients with COVID-19 infection due to multiple factors, such as fever, respiratory insufficiency/hypoxemia, hemodynamic compromise, fear/anxiety, pain, along with several other physical and emotional symptoms [44,45]. Sinus bradycardia and conduction disturbance is another well documented manifestation of covid-19 infection, in which for close monitoring of such cases is mandatory, hence the mechanism is not well understood, however, several factors may...
play a role such as hypoxia, inflammatory injury of the sinus node by circulating cytokines, subsequently, bradycardia may herald an underlying cytokine storm as mentioned in several case reports [47,48,77]. The treatment option varies according to the patient hemodynamic states. Conservative treatment has been effective in stable patients, whilst temporary pacemaker might be considered in case of hemodynamic compromise. Atrial fibrillation (AF) was one of the most encountered cardiac arrhythmias observed in patients with COVID-19 infection, according to a recent survey of electrophysiology professionals. Several mechanisms could be involved in the pathogenesis of AF in these patients; virus- induced cardiac injury that could lead to peri-myocarditis, hypoxemia frequently occurring in these patients, systemic infection [47,49]. the management of AF should be the same as normal population, including synchronized cardioversion for unstable patients, and antiarrhythmic drugs for hemodynamically stable patient. However, extreme cautious is required for drugs that might prolong QT interval. Ventricular arrhythmia including ventricular premature complexes (VPCs), non-sustained VT (NSVT), and sustained VT/VF in the setting of covid-19 infection. Moreover, Special attention is required for the development of polymorphic VT in the form of torsade des pointes (TdP), in the setting of QT prolongation, either pre-existing or acquired and induced by drugs [25]. Keeping in mind that malignant arrhythmia and sudden cardiac death might herald an underlying myocarditis, or ACS.

Heart failure
New onset of HF was observed in as much as a quarter of hospitalized COVID-19 patients; and in as much as one-third of those admitted to the intensive care unit (ICU) [46,63]. As mentioned above. The virus downregulates the angiotensin-converting enzyme 2 (ACE2), leading to increased levels of Angiotensin II causing increased inflammation and hypertension [66]. Elevated natriuretic peptides suggest HF with a worse prognosis of COVID-19 and warrant at least an echocardiogram to further assess cardiac function [65]. It is currently unknown if heart failure is due to new cardiomyopathy or an exacerbation of previously undiagnosed heart failure. It is important to be conscious of this potential cardiac dysfunction when administering intravenous fluids and avoid overaggressive fluid replacement [67]. Be mindful that acute decompensated heart failure is a significant cause of mortality in covid-19 patients with long-term lasting cardiovascular burden.

Takotsubo cardiomyopathy
This condition, also referred to as stress- induced cardiomyopathy, has been described by some authors as a manifestation of covid-19 infection. It is distinguished by acute segmental ventricular dysfunction in a non-coronary distribution. It commonly occurs in reaction to severe emotional or physical stress and can cause significant clinical problems [61]. The pathophysiology of COVID-19-associated TTC may share some features with non-infectious cardiomyopathy and viral myocarditis. Compared with patients with non-TTC myocardial injury and those without myocardial injury, those with TTC had the highest peak levels of cardiac troponin I and creatine-kinase myocardial band. Conversely, the peak levels of inflammatory and pro-thrombotic biomarkers including interleukin-6, ferritin, and d-dimer were the highest among patients with non-TTC myocardial injury [58]. This virus may damage vascular integrity and cause the myocardial abnormalities observed in Takotsubo syndrome. Some authors have reported cases of Takotsubo syndrome associated with CMV infection: the virus may mediate coronary endothelial dysfunction with consequent increased expression of endothelial adhesion molecules and Tran’s endothelial migration within the vasculature. SARS-CoV-2 may exert a direct toxic action on myocytes; indeed, the SARS- CoV-2 spike protein shows high-affinity binding to angiotensin-converting enzyme 2 (ACE2), a human cell receptor which is highly expressed in the heart [62]. There remain questions about the proper treatment of TTS. However, physicians typically utilize ACE inhibitors, beta-blockers, and diuretics for treatment of heart failure. Long-term solutions yet to be known, but indefinite use of beta blockers has been shown to prevent recurrence and decrease the impact of stress hormones [59,60].

Myocardial ischemia
ACS is a recognized complication of COVID-19; its pathophysiology may be related to the hype coagulable state induced by the virus, causing thrombosis of coronary arteries [54]. Severe systemic inflammation increases the risk of atherosclerotic plaque disruption and ACS. Myocardial injury with cytokine release syndrome. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 can elicit the intense release of multiple cytokines and chemokines by the immune system [17,57]. Echocardiography and advanced imaging with cardiac MRI can differentiate myocarditis with diffuse myocardial dysfunction from acute coronary syndromes where a focal wall motion abnormality in the distribution of a specific coronary artery is observed. Furthermore, Spontaneous coronary artery dissection (SCAD) has been reported 4 times up until now in the literature [80-82]. In patients with different ages and risk factors in association with COVID-19. In the context of COVID-19, one of the possible mechanisms for SCAD is that SARS-CoV-2 viral infection can leads into activation of T-cell and infiltration in adventitia and periadventitial fat, which in turn produce more cytokines and proteases, thereby increasing the risk of plaque rupture or erosion and subsequent dissection [48]. A higher index of suspicion of SCAD is warranted in patients with suspected or confirmed COVID-19 presenting with ACS. Medical management of SCAD deviates from standard ACS therapy. In particular, thrombolytic therapy should be avoided for patients with SCAD. Therefore, early coronary angiography to establish SCAD is crucial [56,78]. Angiotensin-converting enzyme inhibitors are administered when there is significant post-MI LV dysfunction (ejection fraction ≤ 40% and class 1 indication). While the use of antplatelet therapies and its duration in the setting of SCAD is still controversial.

Cardiogenic shock
There are several case reports of COVID-19 patients degenerating into cardiogenic shock. In a series of case reports that depicted the various cardiovascular presentations of COVID-19, three out...
of four cases developed cardiogenic shock. The hemodynamic assessment was integral to the recognition of cardiogenic shock in these cases. Consequently, a lower threshold to assess for shock in acute systolic heart failure linked with COVID-19 is critical [68]. Several factors have been linked to the development of cardiogenic shock include Acute MI, acute heart failure, fulminant myocarditis and cardiac tamponade as a consequence of covid-19 infection. N-terminal pro-B-type natriuretic peptide (NT- pro-BNP) will be elevated during an acute decompensation of heart failure. Cardiac catheterization is both the definitive diagnostic investigation and guides therapeutic intervention in Cardiogenic Shock complicating acute myocardial infarction [79].

Pericardial disease:
Pericardial effusion and tamponade secondary to COVID-19 infection have been described in several case reports, either as a presenting symptom or as a late complication [53-55]. TTE is recommended to exclude significant effusion, although the absence of fluid does not rule out active pericarditis. cMRI can describe pericardial thickening or small effusions, which are not appreciated on TTE [53]. However, pericardial involvement is rare with the therapeutic challenge. High-dose aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment; although high-dose aspirin in the management of patients with COVID-19-related acute pericarditis should be individualized, cautious in those with pericardial effusion is justified [50-52]. Since many patients with COVID-19 warrant intubation and mechanical ventilation, it may be reasonable to consider early controlled invasive management of large pericardial effusions to avoid hemodynamic decompensation and the need for emergent pericardiotenesis. It is wise to consider pericardial tamponade as a cause of unexplained deterioration in covid-19 [50].

Conclusion
COVID-19, which has rapidly grown into a pandemic, is associated with a significant cardiovascular burden. There remains poor insight into the cardiovascular sequelae in regards of covid-19 manifestations. Current literature is limited by the lack of reliable and detailed data on the long-term outcome of COVID-19-associated cardiovascular disease. Therefore, survivors from severe COVID-19 are still at increased risk of developing COVID-19 related cardiovascular disease, and there is a reason and need to continue monitoring these patients for cardiac health issues in the long run. Given the worldwide prevalence of this disease and the strong association with CVDs, additional studies and researches are needed to gain a better understanding of the mechanisms that COVID-19 infection variously effect the cardiovascular system. Subsequently, developing tight surveillance is crucial to gain an effective therapeutic intervention against COVID-19-associated CVD.

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