IBOM MEDICAL JOURNAL
Vol.14 No.4 Oct, 2021. Pages 411 - 426
www.ibommedicaljournal.org

Review of cardiovascular involvements in COVID-19

Ekpe EE[1], Umoh IA[2], Shogade T[3], Eyo CS[4], Akpan AF

[1]*Cardiothoracic Surgery Unit, Department of Surgery, Faculty of Clinical Sciences, College of Health Sciences, University of Uyo, Nigeria*
[2&3]*Cardiology Unit, Department of Internal Medicine, Faculty of Clinical Sciences, College of Health Sciences, University of Uyo, Nigeria*
[4]*Department of Anaesthesiology, Faculty of Clinical Sciences, College of Health Sciences, University of Uyo, Nigeria*

Abstract

Background: A spectrum of cardiovascular pathologies occurs in patients with COVID-19 and increases the risk of mortality. Risk of mortality is also heightened in cardiovascular disease patients who contact COVID-19.
Methodology: Online search for the keywords in PubMed, Medline, Embase, Google scholar was done. Relevant research articles yielded from the searches were reviewed.
Results: the searches yielded a total of 172 results, out of which 111 were reviewed. Cardiac involvement was found in 70.6% COVID-19 patients: tachycardia (19%), electrocardiography abnormalities (22%), echocardiography abnormalities (57%), elevated myocardial enzymes (53%), and acute cardiac injury (9%). Eight percent of patients with acute cardiac injury were aged >60 years; 87.5% of them had ≥2 underlying comorbidities (hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease). Novel coronavirus pneumonia was much more severe in the patients with acute cardiac injury than in patients with non-definite acute cardiac injury (P<0.001). Multivariate analyses showed that C-reactive protein (CRP) levels, old age, novel coronavirus pneumonia severity, and underlying comorbidities were the risk factors for cardiac abnormalities in patients with COVID-19.
Conclusion: Besides its prominent expression at the level of the respiratory apparatus, COVID-19 is also characterized by a substantial degree of cardiovascular involvement, both in terms of deterioration of pre-existing conditions, and as the effect of inflammation-facilitated acute events. They include ischemic and inflammatory heart disease, ventricular arrhythmias, conduction disturbances, thrombotic events at the level of the lungs, systemic activation of the coagulation cascade and disseminated intravascular coagulation.

Keywords: COVID-19, Cardiovascular manifestation, cardiac involvement, cardiac affectation

1.0 Introduction

The novel coronavirus disease 2019 (COVID-19) progressed to a pandemic level and affected more than 23 million people in 188 countries as at August 2020.[1] It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of the Coronaviridae family of viruses usually associated with respiratory infections.[2,3] Respiratory manifestations of COVID-19 are well known,[4,5] and recent studies have also observed cardiovascular complications in patients.[6,7] Viral

Corresponding Author: Dr. Eyo E. Ekpe

Cardiothoracic Surgery Unit, Department of Surgery, Faculty of Clinical Sciences, College of Health Sciences, University of Uyo, Nigeria.
E-mail: eyoekpe@uniuyo.edu.ng, Phone: +234(0)8034875889

infection causes increased elaboration of inflammatory biomarkers including interleukin-6 (IL-6)and D-dimer,[8] that influence severe cardiovascular clinical features such as thrombosis and cardiac injury which have been documented in cohorts of COVID-19 patients.[9–11] It is also known outbreaks of acute respiratory infections such as influenza may trigger an increase in coronary deaths due to myocardial infarction or stroke.[12,13] Past viral epidemics like severe acute respiratory syndrome (SARS) had certain cardiovascular complications such as acute myocardial infarction and increased susceptibility to thrombosis.[14,15] In the case of SARS-CoV-2, however, the risk of ischemic stroke has been noted to be 7.5 folds higher than that of influenza patients.[16] Furthermore, emerging evidence from the current COVID-19 pandemic suggests that individuals with preexisting cardiovascular risk factors including heart failure, hypertension, and diabetes may be more susceptible to severe infection and higher fatality rate of covid-19.[4,17–19]

Kevin J. Clerkin, et al noted that SARS-CoV2 invades cells through the angiotensin-converting enzyme 2 receptor. Among patients with COVID-19, there is a high prevalence of cardiovascular disease, and >7% of patients experience myocardial injury from the infection (22% of critically ill patients). Myocardial injury can result from the associated cytokine storm manifested by elevated levels of interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), and D-dimer or myocardial dysfunction from the direct effect of severe acute respiratory syndrome coronavirus 2 on the heart.[20] The SARS-CoV2, similar to previous coronavirus strains, enters human cells through binding protein in angiotensin-converting enzyme 2 (ACE2) that participates in the angiotensin-converting process, which is an important component of cardiovascular modulation and endothelial signalling.[21,22] In addition to the airways and lungs, the cardiovascular system is often involved in COVID-19 early, shown by the release of highly sensitive troponin and natriuretic peptides, capable of prognostic significance, as well as cytokines like interleukin-6.[23]

This present review of cardiovascular involvement in covid-19 attempts to put together the findings from many researches.

2.0 Methodology

Literature search was done using the keywords: "COVID-19, Cardiovascular manifestation, cardiac involvement, cardiac affectation". The search engines were PubMed, Google, Google scholar, Embase, Medline and Hinari. The generated scholarly articles were read and review for appropriateness of content. The relevant studies were reviewed for cardiovascular involvement in COVID-19. The various studies were summarized according to their findings.

3.0 Results

The searches yielded a total of 172 results, out of which 111 were reviewed. The main findings are summarized in the discussion.

4.0 Discussion

4.1 Relationship between SARS-CoV2 and cardiovascular system

The SARS-CoV2, like other coronavirus strains, enters human cells through the spike protein binding to the angiotensin-converting enzyme 2 (ACE2).[22] This enzyme participates in the angiotensin-converting process, which is an important component of cardiovascular modulation and endothelial signalling. Moreover, the ACE2 has an innate role in binding to cell membranes, which enables virus replication in the intracellular space.[22,24] As ACE2 is highly expressed in lung tissue, most of the manifestations of COVID-19 are related to respiratory symptoms. The ACE2 pathway of SARS-CoV2 largely affects the alveolar epithelial cells, leading to local damage and inflammation. The alterations evolve with increased capillary permeability, interstitial edema, and thickening of the alveolar-capillary membrane. The infection mechanism of SARS-CoV2 explains the observation of acute lung injury and hypoxia in a significant number of cases. Also, the ACE2 tends to present higher levels in patients with cardiovascular disease, particularly because of the drugs used to control the renin-angiotensin-aldosterone system (RAAS) that usually increases the availability of this aminopeptidase.[25] The inflammatory response to SARS-CoV2 comprises two main stages.[26] The primary inflammatory response is mediated by apoptosis of epithelial and endothelial cells, releasing a vast proinflammatory content. Also,

continuing viral replication causes a downregulation of ACE2 which reduces the protective role of this enzyme and leads to a dysfunction of the renin-angiotensin system with a further increase in vascular permeability and pulmonary cell infiltration. As macrophages and lymphocytes respond to the chemotaxis, there is a pyroptosis by internal replication of the virus, and the event explains the lymphopenia found in a significant number of patients. The secondary wave of the inflammatory response initiated with the expression of neutralizing antibodies (NAb) as an adaptive immunity; this stage is critical for patients to develop severe manifestations of COVID-19. The NAb activation enhances the Fc receptors related to IgG potentializing the inflammatory response. Why an increase in IgG expression exposes more the patients to a severe presentation of SARS-CoV2 infection is unclear. One possible hypothesis is that antibody-dependent enhancement of viral infection evolves into persistent viral replication and explains an overwhelming inflammatory response from macrophages.[25,26] As described earlier, viral replication leads to a downregulation of ACE2, which is an important tissue protector.[27] Therefore, discussions about the pros and cons of withdrawing ACE inhibitors and angiotensin receptor blockers (ARBs) in cardiovascular patients have been made to reduce the risk of a severe COVID-19 manifestation.[28,29] Further studies are necessary to understand whether these medications make patients more susceptible or whether its continuation has an essential protective role.

4.2 Pathogenetic mechanism of myocardial injury

Recent reports have observed an elevation of brain natriuretic peptide, creatine kinase (CK), and in some cases, increased troponin I in patients with SARS-CoV2 infection.[30-35] In a cohort of 150 patients, Ruan et al.[36] identified that myocardial damage/heart failure contributes to death combined with respiratory failure in 33% of cases and myocardial damage with circulatory failure in 7%. These observations reveal a myocardial injury during severe manifestations of the disease. It is well established that a severe respiratory infection and a scattered inflammatory process can cause non-ischemic myocardial injury, including the evolution to myocarditis. The presence of myocardial injury was also detected as electrocardiographic and echocardiographic abnormalities. This event is expressed in up to 17% of total hospitalized patients during COVID-19, and up to 59% in cases of death.[2,37] Recent reports have identified the occurrence of myocarditis with a global decrease in ventricular function, observed by lower left ventricular ejection fraction in patients with SARS-CoV2 infection. Moreover, Liu et al.[38] reported a case of fulminant myocarditis and, interestingly, pathological investigations of this case report did not find an obvious histological finding, such as nuclear or cytoplasmic viral inclusions into myocardial fibers. This observation suggests that heart damage may not be directly related to the SARS-CoV2 replication in the myocardial tissue.[39] It may be possible that myocardial injury is the result of a supply-demand mismatch and additional damage caused by microembolization of the coronary arteries, triggering peripheral and silent myocardial ischemia. Nonetheless, these assumptions must be investigated in further histological investigations and future cohort monitoring. Finally, acute respiratory infection (ARI) severity may be related to an increased risk of a classic myocardial infarction event. It is well known that greater inflammatory responses in the endothelium could enhance susceptibility to the rupture of unstable atherosclerotic plaques. Therefore, the incidence of myocardial infarction among cardiovascular disease patients is increased after a viral ARI, including the coronavirus (Incidence Ratio: 3.30 [1.90–5.73]).[40] We also suggest a closer monitoring of cardiocirculatory function in severe cases of ARI, especially in patients with precedent cardiovascular disease. Therefore, the lethality of COVID-19 is related to cardiac failure with subsequent multiple organ dysfunction. Early strategies that guide clinical decisions can be lifesaving and prevent myocardial damage.

4.3 Pathogenetic mechanism of myocardial injury with disseminated intravascular coagulation

Disseminated intravascular coagulation (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.[41] A marker of severe sepsis, DIC further perpetuates multiorgan damage through thrombosis, reduced perfusion, and bleeding, DIC has been implicated in the thrombosis of coronary arteries (epicardial vessels and microvasculature), focal necrosis of the myocardium, and severe cardiac dysfunction.[42] Myocardial injury with DIC has been recently reported in two critically ill patients with COVID-19.[43] Both patients had significantly elevated Tn and brain natriuretic peptide, which returned to normal after treatment with heparin, mechanical ventilation, and antiviral agents.

4.4 Pathogenetic mechanism of non-ischaemic myocardial injury

Myocarditis and stress-induced cardiomyopathy Myocardial injury from SARS- CoV-2 infection may also be mediated by non-ischaemic mechanisms, such as acute and fulminant myocarditis and stress- induced cardiomyopathy. The distinction between myocarditis and stress-induced cardiomyopathy can be challenging, since cardiovascular magnetic resonance (CMR) and/or biopsy are not available in most cases. Fried et al and Sala et al each reported a patient with COVID-19 with mid- left ventricular (LV) or basal-to-mid LV hypokinesis, a pattern of mid- ventricular, or reverse Takotsubo stress cardiomyopathy, respectively.[7,37] The incidence of acute heart failure was 33% (7/21) in critically ill patients with COVID-19 without a past history of LV systolic dysfunction in Washington state.[44] Importantly, cardiomyopathy can develop in COVID-19 with mild or absent respiratory symptoms.[45]

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.[3,46] Cytokine release syndrome ('cytokine storm'), is a poorly understood immunopathological process caused by hyper-induction of proinflammatory cytokines such as interleukin (IL)-1, IL-6, T helper 1 cytokine interferon- gamma, and tumour necrosis factor-alpha (TNF-α), has been reported in the setting of SARS, MERS, and influenza.[47-49] It is postulated that proinflammatory cytokines depress myocardial function immediately through activation of the neural sphingomyelinase pathway and subacutely (hours to days) via nitric oxide- mediated blunting of beta- adrenergic signalling.[50] Accumulating evidence suggest that a subgroup of patients with severe COVID-19 can develop cytokine storm.[51] Plasma levels of IL-1β, IL-6, IL-8 and TNF-α have been found to be significantly higher in patients with COVID-19.[3] 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.[52]

4.5 Pathophysiology of cardiac injury

SARS-CoV-2 is an enveloped, positive- sense single- stranded RNA virus.[53] SARS-CoV-2 and other similar coronaviruses use the ACE 2 (ACE2) protein for ligand binding before entering the cell via receptor- mediated endocytosis.[54] Recent data on viral structure reveal that SARS- CoV-2 has tighter interaction with the human ACE2 receptor binding domain as compared with SARS-CoV, which may explain in part the greater transmissibility of the current virus among humans.[55] ACE2 is a membrane protein that serves many physiological functions in the lungs, heart, kidneys and other organs.[56] It is highly expressed in type 2 lung alveolar cells, which provides an explanation for the respiratory symptoms experienced by patients with COVID-19.[57] More than 7.5% of myocardial cells have positive ACE2 expression, based on single- cell RNA sequencing,[14] which could mediate SARS-CoV-2 entry into cardiomyocytes and cause direct cardiotoxicity. The mechanisms of cardiovascular injury from COVID-19 have not been fully elucidated and are likely multifactorial. SARS-CoV-2 viral particles have been identified by RT-PCR in cardiac tissue in some cases,[15] supporting that direct cardiotoxicity may occur. Virally driven hyperinflammation with cytokine release may lead to vascular inflammation, plaque instability, myocardial inflammation, a hypercoagulable state, and direct myocardial suppression.[16,17,58-60] Other systemic consequences of COVID-19 infection, including sepsis and disseminated intravascular coagulation (DIC), may also mediate cardiac injury. Based on postmortem biopsies, the pathological features of covid-19 in multiple organs greatly

resemble those seen in SARS[18,19] and MERS.[20,21] In cardiac tissue, pathological findings vary from minimal change to interstitial inflammatory infiltration and myocyte necrosis. In the vasculature, micro-thrombosis and vascular inflammation could be found.

Acute cardiac injury, defined as significant elevation of cardiac troponins, is the most commonly reported cardiac abnormality in COVID-19. It occurs in approximately 8–12% of all patients. Direct myocardial injury due to viral involvement of cardiomyocytes and the effect of systemic inflammation appear to be the most common mechanisms responsible for cardiac injury.[61-70]

4.6 Manifestations of cardiac involvement

Cardiac injury is a common problem associated with COVID-19.[24,70-75] Acute coronary syndrome (ACS), arrhythmias, and blood pressure fluctuations have been reported to occur, in addition to cardiac dysfunction. The incidence of arrhythmia has not been clearly reported, although it is expected to be more frequently seen in critically ill patients; these include tachyarrhythmia, bradyarrhythmia, and asystole.[16,25,76-90] In a study conducted in Wuhan, cardiac conditions, including heart failure (HF), contributed to 40% of the mortality, either acting alone or in conjunction with respiratory failure.[15]

COVID-19 patients with pre-existing cardiovascular disease are counted in greater frequency in intensive care unit settings, and ultimately suffer greater rates of mortality. Other studies have noted cardiac presentations for COVID-19, rather than respiratory, such as acute pericarditis and left ventricular dysfunction. In some patients there has been evidence of acute myocardial injury, with correspondingly increased serum troponin I levels.[52,91-96]

Huayan Xu, et al[53] noted that cardiac involvement was found in 72 of the 102 (70.6%) patients: tachycardia (n=20), electrocardiography abnormalities (n=23), echocardiography abnormalities (n=59), elevated myocardial enzymes (n=55), and acute cardiac injury (n=9). Eight patients with acute cardiac injury were aged >60 years; seven of them had ≥2 underlying comorbidities (hypertension, diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease). Novel coronavirus pneumonia was much more severe in the patients with acute cardiac injury than in patients with nondefinite acute cardiac injury (P<0.001). Multivariate analyses showed that CRP (C-reactive protein) levels, old age, novel coronavirus pneumonia severity, and underlying comorbidities were the risk factors for cardiac abnormalities in patients with COVID-19.

4.7 Manifestations of cardiovascular involvement

The clinical cardiovascular manifestations of COVID-19 include elevation of cardiac biomarkers (ischaemic or non- ischaemic aetiology), cardiac arrhythmia, arterial and venous thromboembolism (VTE), and cardiogenic shock and arrest.97 Myocardial injury is common among patients with COVID-19 infection and correlates with disease severity. Although somewhat variable, studies on patients with COVID-19 have generally defined myocardial injury as the elevation of high-sensitivity cardiac troponin (hs-cTn) above the 99th percentile of its upper limit of normal or evidence of new electrocardiographic or echocardiographic abnormalities.[3,98] Increased levels of hs-cTn correlate with disease severity and mortality rate in COVID-19, even after controlling for other comorbidities.[99] The pattern in the rise of cTn levels is also significant from a prognostic standpoint. Non- survivors had a higher level of Tn elevation which continued to rise until death (mean time from symptom onset to death was 18.5 days (IQR 15–20 days)), while Tn levels for survivors remained unchanged.[100] This finding may support the monitoring of cTn levels every few days in hospitalised patients. It is a challenging task to differentiate potential aetiologies of cardiac injury: acute coronary syndrome (ACS) due to plaque rupture or thrombosis (type I myocardial infarction (MI)) or supply-demand mismatch (type II MI), myocardial injury due to DIC, and non-ischaemic injury (myocarditis, stress-induced cardiomyopathy, or cytokine release syndrome).[101]

Ischaemic myocardial injury Myocardial infarction Severe viral infections can cause a systemic inflammatory response syndrome that increases the risk of plaque rupture and thrombus formation, resulting in either an ST- elevation MI or non-ST-

elevation MI.[24] In a study of 75 patients hospitalized with SARS, acute MI was the cause of death in two of five fatal cases.[102] There is also a significant association between acute MI and influenza. As compared with the prevalence of acute MI occurred 1 year before or 7 days to 1 year after influenza, the incidence ratio of acute MI within 7 days of influenza infection was 6.1 (95% CI: 3.9 to 9.5).[103] Although reports of type I MI in patients with COVID-19 have not yet been published, anecdotal report was presented.[104] Treatment of ACS in COVID-19 should be according to the updated Society for Cardiovascular Angiography and Interventions guidelines.[105] Severe respiratory viral infections can also lead to decreased oxygen delivery to the myocardium via hypoxaemia and vasoconstriction, as well as the haemodynamic effects of sepsis with increased myocardial oxygen demand. This supply and demand mismatch may lead to sustained myocardial ischaemia in patients with underlying coronary artery disease. However, a rise and/or fall of hs-cTn is not sufficient to secure the diagnosis of acute MI as seen in MI with non-obstructive coronaries, even in the absence of COVID-19. Therefore, the diagnosis of acute MI should also be based on clinical judgement, symptom/signs, ECG changes, and imaging studies.

4.8 Pathogenetic mechanism of cardiovascular involvement

Many patients with COVID-19 have evidences of myocardial damage. Shi et al[10] reported that among 416 hospitalized patients with confirmed COVID-19, 19.7% had myocardial injury which were manifested by elevated high-sensitivity troponin-I levels. Patients with myocardial injury had a significant higher inhospital mortality rate (51.2%) compared with those without (4.5%).[19] Guo et al[106] also presented a cohort of 187 hospitalized with confirmed COVID-19 and a total of 27.8% had myocardial injury as manifested by elevated troponin-T levels. Similarly, mortality was significantly higher in those with elevated troponin T levels than those with normal troponin-T levels (59.6% vs 8.9%, respectively; $p < 0.001$). Higher mortality was found in those with elevated troponin T levels in preexisting CVD (64.4%) and without prior CVD (37.5%), indicating that myocardial injury was correlated with the risk of mortality. Similar findings were also observed in western population. In a series of patients from Seattle, patients with evidence of cardiac involvement had a marked increase in mortality.[21] In addition, during the internalization process of COVID-19 into human cell, activated macrophages can release cytokines, which will promote the expression of adhesion molecules for endothelial activation, inflammatory cell infiltration, and vascular inflammation. The dysfunctional endothelium becomes pro-adhesive and pro-coagulant. The activated macrophages can also release procoagulant factors, such as plasminogen activator that further accelerates vascular inflammation and enhances a prothrombotic state, and this is often seen with high d-dimer levels in COVID-19 infection. The presence of microangiopathy and microthrombi leads to micro-infarcts within the cardiac tissue and also contributes to plaque rupture and acute myocardial infarction.[8] In addition to intracoronary plaque rupture, myocardial injury could result from other reasons. From a series of 18 patients with ST-segment elevation in New York with confirmed COVID-19, only six (67%) of nine patients who received coronary angiography had obstructive disease and five (56%) underwent percutaneous coronary intervention (one after the administration of fibrinolytic agents.[22] Increased troponin value represents evidence of myocardial injury and these may come from cytokine storm, hypoxic injury, coronary spasm, microthrombi, myocarditis, or true plaque rupture.[23,106] Severe infections could cause hypoxia and hypoperfusion to vital organs which predispose patient to thrombotic events.[24] Guo et al demonstrated additional insights that patients with high troponin T levels are associated with higher levels of CRP, procalcitonin, d-dimer, NT-proBNP, and greater leukocyte counts, indicating that myocardial injury was correlated with the severity of inflammation.[106] From previous influenza epidemics, more patients die of cardiovascular events than respiratory involvements.[25] Viral infections can trigger acute coronary syndrome, arrhythmias, and exacerbation of heart failure, owing to combination of systemic inflammatory response and localized arterial inflammation.[26,27] Systemic inflammation or hypoxemia resulted from COVID-19 may also induce atrial/ ventricular arrhythmia, most

commonly atrial fibrillation, which may raise the issue of anticoagulants usage.[28] Severe inflammation could also cause hemostatic abnormalities including disseminated intravascular coagulation (DIC), pulmonary microthrombi formation, and intravascular coagulopathy.[24]

Tang et al reported increased level of d-dimer and fibrin degradation products ([FDPs], ~3.5- and ~1.9-fold increase, respectively) and prothrombin time prolongation (by 14%, $p < 0.001$) in mortality cases than survivors after COVID-19.[86] In addition, 71% of COVID-19 patients who died fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC, compared with only 0.6% among survivors.[24,29] Furthermore, a small proportion of patients may have direct cardiac involvement including cardiomyopathy, myocarditis, or heart failure. One COVID-19 case was reported to have myocarditis with reduced systolic function and marked biventricular myocardial interstitial edema according to cardiac magnetic resonance images.[30] Sporadic autopsy cases also showed infiltration of interstitial mononuclear inflammatory cells within myocardium.[31] Endomyocardial biopsy done in a COVID-19 patient with cardiogenic shock showed viral particles in the myocardium, suggesting the damages could either come from viremic phase or migration of infected macrophages.[32] The presence of cardiac injury and stress, as evidenced by altered biomarkers including troponin, natriuretic peptides, and coagulation parameters, indicates a poor prognosis of COVID-19. On the other hand, close monitoring of these biomarkers could help early detections of cardiac injury and possibly prevent further deterioration with appropriate management if available.

4.9 Summary of cardiovascular effects

Previous viral epidemics have been associated with a significant increase in the incidence of myocarditis, cardiomyopathy, HF, MI, arrhythmias, and sudden cardiac death.[26-28] It was therefore not unexpected to see a higher incidence of CV events in those infected with COVID-19. On the other hand, the presence of pre-existing cardiac conditions appears to increase the chance of complications, including death, in COVID-19 patients. As reported in a meta-analysis of patients admitted with COVID-19, the incidence of CV disease (CVD) was 16.4% in non-intensive care unit (ICU) patients, and three times higher in those requiring the ICU.[29] In the following sections, we highlight various baseline CV comorbidities and disorders that have been reported to date with COVID-19.

4.10 Pathophysiology of myocardial Damage

Cardiotropic viruses directly attack cardiac cells at the initial phase, followed by a secondary inflammatory response that can lead to further cardiac damage. It is likely that coronavirus is following a similar pathway. Indeed, the ACE2 receptor plays a role in the direct cardiac damage, as well as vascular involvement in COVID-19 infection. In autopsies from the SARS outbreak in 2002, 35% of heart samples revealed the presence of viral RNA in the myocardium, and it was associated with reduced ACE2 expression. It is believed SARS-CoV-2 may share the same mechanism, with direct cardiac muscle damage playing a role in both the myocarditis and HF in COVID-19-infected individuals. Cardiac muscle involvement has been evident by increased cardiac biomarkers in a sizable portion of patients.[42] Additionally, autopsy studies of COVID-19 have demonstrated the presence of mononuclear infiltrate in the myocardium, with related cardiomyocyte necrosis.[43] Finally, acute lung injury and ARDS result in right heart strain, with right ventricular (RV) dilation and dysfunction, and high positive end expiratory pressure (PEEP) use while on ventilation can also worsen cardiac function.[44] Many studies have shown poorer outcomes, including mortality, in patients with elevated biomarkers (such as cardiac troponin, creatine kinase, pro-brain natriuretic peptide [BNP]) in COVID-19-related ARDS.[45,46] In a prospective cohort study of 179 patients with COVID-19 pneumonia, a cardiac troponin I level of ≥ 0.05 ng/mL was found to be strongly associated with increased mortality (hazard ratio [HR] 4.077, 95% confidence interval [CI] 1.166–14.253; $p < 0.001$).[47] In another study of 273 patients, cardiac biomarkers (N-terminal [NT] pro-BNP, cardiac troponin, and myoglobin) were significantly higher in severe and critical cases compared with mild cases.[48] Another study aimed at correlating the change in troponin levels with the progression of COVID-19 disease, and showed that 37.5% of

patients with normal troponin at admission had a rise in troponin during hospitalization, which peaked in the week before demise.[49] A meta-analysis of 341 patients in China confirmed the findings of these studies, reinforcing the importance of troponin measurement at admission and/or during hospitalization to determine the severity of the disease. Importantly, troponin can be elevated in COVID patients with underlying renal impairment.[42] In this setting, elevations of other cardiac biomarkers will be more reliable as an indicator of underlying cardiac injury. Zhou et al[75] and Li et al[105] have described increased levels of creatine kinase–myocardial band (CK-MB), myoglobin, and NTpro-BNP in COVID patients, which also correlated with the severity of disease. EKG and echocardiographic findings, in conjunction with biomarker elevation, help diagnose and predict prognosis in COVID-19 patients with cardiac involvement. Notably, data on the correlation between biomarkers, clinical manifestations and echocardiographic findings are lacking, and further study of this relationship may ultimately help in early risk stratification.[52] Although case reports of myocarditis in COVID-19 patients exist, it is unclear whether the myocarditis is induced by the virus directly or results from an inflammatory response.[53] A case of myopericarditis complicated by cardiac tamponade was also reported in the literature.[54] Isolated hemorrhagic pericardial effusion with tamponade without the features of myocarditis has also been demonstrated.[55] Recently, two cases have been reported with apparent Takotsubo syndrome in the setting of COVID infection.[56,57] Although cardiac involvement usually occurs later in the course of COVID-19, acute HF secondary to myocardial involvement or previously existing cardiac disease could be the presenting symptoms in COVID-19 infection in almost one-quarter of patients. The management of myocardial dysfunction in COVID-19 leading to HF is similar to other forms of HF. Optimization of fluid balance, monitoring of electrolytes and renal function, and early use of the cardiac catheterization laboratory and invasive monitoring all play important roles in managing COVID patients with HF.[58]

4.11 Pathogenetic mechanism of coronary ischemia and infarction

Coronary involvement and ischemia have been seen, including ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), with several mechanisms explaining coronary artery involvement. As ACE2 is expressed in vascular endothelial cells, direct viral infection can lead to plaque instability and type 1 MI. Plaque instability and rupture may also result from the severe systemic inflammatory response in the third phase of the disease. COVID-19 can additionally precipitate type II MI by demand ischemia as patients get sicker. Hypoxia secondary to lung involvement, and fever and tachycardia secondary to sepsis, further worsen the cardiac function. Coronary artery involvement can further be produced by a microangiopathy that has also been described. Such small vessel involvement can be due to systemic vasculitis or to microembolization from ACS or disseminated hypercoagulability impairing blood flow.[42]

4.12 Pathogenetic mechanism of arrhythmias

Arrhythmia could be the first presentation of COVID-19, and new-onset and/or progressive arrhythmia could indicate cardiac involvement.[106,107] A study of 137 patients in Wuhan showed that 7.3% had experienced palpitations as one of their presenting symptoms for COVID-19.[42] Arrhythmias were found to be more common in intensive care unit (ICU) patients with COVID-19 (44.4%) than non- ICU patients (6.9%).[4] Patients with elevated Tn also had a higher incidence of malignant arrhythmia (ventricular tachycardia or ventricular fibrillation) than those with normal Tn levels (11.5% vs 5.2%, $p<0.001$).[6]

The incidence of arrhythmia is currently unknown in COVID-19 patients, with preliminary data suggesting an incidence of 16.7% among hospitalized patients and 44.4% of ICU admissions.[16] Both ventricular and atrial arrhythmias have been seen, in addition to sinus tachycardia due to clinical decompensation, fever, or sepsis. The cause of arrhythmia could be myocarditis, hypoxia, or electrolyte derangement seen in these patients, and in many cases may be reactive. Management of these arrhythmias are largely supportive, with control of the underlying clinical condition, electrolyte repletion, and

pharmacologic antiarrhythmic therapy. Specific mention should be made regarding drugs to treat COVID-19 and the potential for pro-arrhythmia. Although data on outcomes with hydroxychloroquine are not available, it is widely used in hospitals for critical patients. The drug is a known inhibitor of the potassium channel Kv11.1 present in the heart, potentially increasing the QTc interval and predisposing the patient to fatal ventricular tachyarrhythmias (torsades de point). In the setting of a very long half-life of 40 days, this adverse effect is rarely seen in clinical practice in patients routinely treated for malaria and rheumatological conditions such as systemic lupus erythematosus,[62,63] but the incidence alongside COVID-19, especially in severe cases, remains unclear. According to the recommendations from the Heart Rhythm Society released recently in collaboration with the ACC and AHA, hydroxychloroquine use must be closely monitored in certain patient groups. These include individuals with a known history of long QT syndrome, those with deranged renal function, those with electrolyte abnormalities such as hypokalemia and hypomagnesemia, and those prescribed other QTc-prolonging drugs.[64] When administered in combination with azithromycin, which is also known to prolong the QTc interval, dose adjustments may be necessary.[65] Recently, the US FDA has mentioned the risk of this combination therapy which include arrhythmias leading to cardiac arrest.[66,67]

4.13 Pathogenetic mechanism of venous thromboembolism

Due to prolonged immobilization, hypercoagulable status, active inflammation, and propensity for DIC, patients with COVID-19 are at increased risk of VTE. The prevalence of ultrasound- confirmed deep venous thrombosis in patients with COVID-19 is 22.7%[43] and 27% in ICU patients.[44] Patients with COVID-19 have been shown to have significant higher level of D- dimer, fibrin degradation products (FDP), and fibrinogen, compared with healthy controls.[45] In addition, D-dimer and FDP titres were higher in patients with severe COVID-19 than those with milder disease.[45] A retrospective, multi-centre cohort study demonstrated that D-dimer >1 μg/mL on admission was associated with in- hospital death (OR: 18.4, 95% CI: 2.6 to 128.6, p=0.003).[22] Thus, in the setting of critically ill COVID-19 patients with clinical deterioration, VTE (including pulmonary embolism) should be considered.

An increased risk of blood clot formation resulting from hypercoagulability has been previously noted with SARS and MERS.[68] Similarly, COVID-19 has been associated with a hypercoagulable state. Dysfunction of endothelial cells induced by infection results in excess thrombin generation and fibrinolysis shutdown. The hypoxia found in severe COVID-19 can also stimulate thrombosis through increasing blood viscosity. Hypoxia-inducible transcription factor-dependent signaling pathway also plays a role in increasing the coagulability of the blood.[69] A study by Panigada et al. showed an increased risk of venous thrombosis in COVID-19-affected individuals.[87] One study involving 184 patients showed CT angiography and/ or ultrasonography confirmed venous thromboembolism (VTE) in 27% of patients and arterial thrombotic events in 3.7% of patients. PE was the most frequent thrombotic complication and may be massive with significant RV failure.[71] The diagnosis of VTE and PE in COVID patients is challenging. The International Society on Thrombosis and Hemostasis (ISTH) advocates the use of laboratory tests, including d-dimers, prothrombin time, and platelet count, to stratify patients at risk of increased blood clot formation;[72] however, elevated d-dimer levels are not specific to the diagnosis of VTE. If only a high d-dimer level is relied on for diagnosis, it will unnecessarily increase the utilization of CT angiography for infected patients, without much benefit. In addition, it may worsen kidney function due to contrast use in the setting of poor cardiac output and hypoxia from COVID-19.[73] Maintaining isolation while doing the tests is also another hurdle for hospitals. Echocardiogram may aid in the diagnosis of large PE by finding isolated RV dilation or failure, or a saddle PE, although it may be difficult to visualize.[74] Prophylaxis with low-molecular-weight heparin (LMWH) is recommended for every patient, if not contraindicated.[72] In a study involving 449 patients with severe COVID-19, anticoagulant therapy, mainly with LMWH, was associated with lower mortality in patients with markedly elevated D-

dimer.[75] The use of unfractionated heparin may be superior in critically ill patients with underlying renal failure, which is a contraindication to LMWH. Interestingly, in vivo models of coronavirus infection have shown that administration of unfractionated heparin functions as a decoy receptor, reducing viral infectivity and potentially augmenting viral clearance.[76] Heparin also has anti-inflammatory effects, reduces myocardial inflammation, and has shown antiviral effects in animal models.[77] Tissue plasminogen activator (TPA) has shown transient improvement in a case series but there is still a lack of data regarding the safety of use in this setting. Furthermore, there have been no data on the adequate dose of TPA.[78] Direct-acting oral anticoagulants (DOACs) can also be considered in the treatment of thromboembolism in COVID19 infection. However, drug interactions between DOAC and antiviral treatments, as well as dosing concerns in the setting of changing kidney function, need to be considered before prescribing these drugs.[79] Asakura et al. have proposed the use of nafamostat, a synthetic serine protease inhibitor, as a short-acting anticoagulant with antiviral properties, along with heparin, in COVID patients; more data are required regarding the efficacy of this agent.[97] A study has shown an increased incidence of VTE even in anticoagulated patients, but the small sample size and retrospective nature are two limitations of that study.[81] Recently published clinical data have suggested that systemic anticoagulation may be associated with positive outcomes among patients hospitalized with COVID-19, but that study has some limitations, including its observational nature and unobserved confounding factors.[82]

4.14 Effects of Antihypertensive Medications

It is estimated that 15-30% of COVID-19 patients have hypertension (HTN).16 Indeed, a meta-analysis (n = 46,248) including eight studies from China demonstrated that the most common cardiac comorbidity was HTN (17 ± 7%, 95% CI 14-22%).[100] ACE2 receptor expression is similar in adipose and non-adipose tissues, but as obese individuals have more adipose tissue in the body, they may have an increased number of receptors. Although some have reported obesity to be a risk factor for COVID infection, more data are required to see if obese individuals are indeed more vulnerable.[84] Given the prevalent use of ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs), and the predominant role of ACE2 receptors in the disease pathogenesis, there has been some concern surrounding the use of these medications in COVID-19 patients. Animal data have supported that chronic use of ARBs elevates ACE2 receptor expression, and elevated ACE2 expression has potential protective CV effects.[85] Zhang et al. recently published a retrospective, multicenter study including 1128 adult patients with COVID-19 and found a lower risk of all-cause mortality with inpatient use of ACEIs/ARBs compared with ACEIs/ARBs non-users.[103] Jarcho et al. have highlighted three more recently published studies, showing no evidence of increased risk of infection or inpatient mortality in COVID-affected patients who continued on these medications.104 Another recent study has shown similar confirmation.105 Based on available data, most of the major society guidelines have recommended against stopping ACEIs/ARBs in patients already taking these medications, or initiating these medications in newly diagnosed patients.[106-108]

4.15 Effects of drugs used in treatment of COVID-19 and their cardiovascular adverse effects

A host of therapeutic agents have been employed to treat patients with COVID-19, however a detailed review of these is beyond the scope of this review. We focus on the most promising drugs that have been repurposed and used to treat this disease, emphasizing the CV adverse effects of these therapies and the known strategies to counter them. Among the treatments employed, chloroquine and hydroxychloroquine, antiretrovirals (lopinavir and ritonavir), ribavarin, remdesivir, corticosteroids, anti-cytokine agents (IL-6 inhibitors), and immunoglobulin therapy (convalescent plasma) have been prominent.[109,110] Chloroquine and hydroxychloroquine have been used to treat patients with COVID-19 in small randomized clinical trials and are postulated to work by blocking viral entry into cells through endosomal trafficking and by exerting an immunomodulatory effect through cytokine attenuation. Both agents can cause QTc prolongation, as previously discussed, which can be

aggravated by concomitant use of azithromycin, a macrolide antibiotic, and other fluoroquinolones. Baseline electrocardiography is recommended in patients to evaluate for prolonged QTc in specific high-risk populations, as previously discussed. Serial electrocardiography is need for monitoring in critically ill patients following the initiation of these medications.[65] Lopinavir and ritonavir also have the potential to cause QTc prolongation.[111] Ribavirin has the potential to cause hemolytic anemia in high doses, which can also increase CVD risk and hemodynamic instability.[112]

5.0 Conclusion

Besides its prominent expression at the level of the respiratory apparatus, COVID-19 is also characterized by a substantial degree of cardiovascular involvement, both in terms of deterioration of pre-existing conditions, and as the effect of inflammation-facilitated acute events. They include ischemic/inflammatory heart disease, ventricular arrhythmias, conduction disturbances, thrombotic events at the level of the lungs, and systemic activation of the coagulation cascade, configuring the scenario of disseminated intravascular coagulation.

References

1. Gencer S, Lacy M, Atzler D, van der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. Thromb Haemost 2020;120:1629–41.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(05): 533–534.
3. Cheng VCC, Lau SKP, Woo PCY, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and re-emerging infection. Clin Microbiol Rev 2007;20(04):660–94.
4. Guan WJ, Ni ZY, Hu Y. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–1720.
5. Lovato A, de Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. Ear Nose Throat J 2020. Doi: 10.1177/0145561320920762.
6. Inciardi RM, Lupi L, Zaccone G. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5(07):819–24.
7. Sala S, Peretto G, Gramegna M. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020;41(19): 1861-2.
8. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thromb Haemost 2020;120(05):876–78.
9. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J 2020;41(19):1858.
10. Shi S, Qin M, Shen B. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(07):802–810.
11. Cowan LT, Lutsey PL, Pankow JS, Matsushita K, Ishigami J, Lakshminarayan K. Inpatient and outpatient infection as a trigger of cardiovascular disease: the ARIC study. J Am Heart Assoc 2018;7(22):e009683.
12. Madjid M, Miller CC, Zarubaev VV. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8years of autopsies in 34,892 subjects. Eur Heart J 2007;28(10): 1205–10.
13. Peiris JSM, Chu CM, Cheng VCC. HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361(9371):1767–72.
14. Chong PY, Chui P, Ling AE. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. Arch Pathol Lab Med 2004;128(02):195–204.
15. Merkler AE, Parikh NS, Mir S. Risk of ischemic stroke in patients with Covid-19 versus patients with influenza. MedRxiv 2020. Doi: 10.1101/2020.05.18.20105494.

16. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395 (10223):497–506.
17. Wang D, Hu B, Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–9.
18. Zhu L, She ZG, Cheng X. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type2 diabetes. Cell Metab 2020;31(06):1068–77.
19. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13): 1239–42.
20. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation 2020; 141:1648-55.
21. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27:e201017. doi: 10.1001/jamacardio.2020.1017.
22. Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19; Implications for the Cardiovascular System. Circulation 2020;142:68-78 https://doi.org/10.1161/CIRCULATIONAHA.120.047549.
23. Rocco IS, Walter J. Gomes WJ, Viceconte M, Bolzan DW, Moreira RSL, et al. Cardiovascular involvement in COVID-19: not to be missed. Braz J Cardiovasc Surg 2020;35(4):530-8.
24. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25(6):291-4. doi: 10.1016/j. tips.2004.04.001.
25. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. Virol Sin. 2020 Mar 3. doi: 10.1007/s12250-020-00207-4.
26. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020;382(17):1653-9. doi: 10.1056/NEJMsr2005760.
27. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. 2020 May 1. doi: 10.1056/NEJMoa2007621.
28. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med. 2020 Mar 20:S2213-2600(20)30127-2. doi: 10.1016/S2213-2600(20)30127-2.
29. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Feb 24. doi: 10.1016/S2213-2600(20)30079-5. Epub ahead of print. Erratum in: Lancet Respir Med. 2020 Apr;8(4):e26.
30. Wang YD, Zhang SP, Wei QZ. [COVID-19 complicated with DIC: 2 cases report and literatures review]. Zhonghua Xue Ye Xue Za Zhi 2020;41:E001.
31. Arentz M, Yim E, Klaff L. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA 2020. doi:10.1001/jama.2020.4326. [Epub ahead of print: 19 Mar 2020].
32. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-422. doi: 10.1016/S2213-2600(20)30076-X. Epub 2020 Feb 18. Erratum in: Lancet Respir Med. 2020 Feb 25.
33. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial Infarction after LaboratoryConfirmed Influenza Infection. N Engl J Med. 2018;378(4):345-353. doi: 10.1056/NEJMoa1702090.
34. Tang N, Li D, Wang X. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844–7.
35. Sugiura M, Hiraoka K, Ohkawa S. A clinicopathological study on cardiac lesions in

64 cases of disseminated intravascular coagulation. Jpn Heart J 1977;18:57–69.
36. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 Mar 3:1–3. doi: 10.1007/ s00134-020-05991-x. Epub ahead of print. Erratum in: Intensive Care Med. 2020 Apr 6.
37. Fried JA, Ramasubbu K, Bhatt R. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930-6.
38. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020 Mar;63(3):364-374. doi: 10.1007/s11427-020-1643-8.
39. Zhou P, Yang X- L, Wang X- G. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
40. Hoffmann M, Kleine- Weber H, Schroeder S. SARS- CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020. doi:10.1016/j.cell.2020.02.052.
41. Shang J, Ye G, Shi K. Structural basis of receptor recognition by SARS- CoV-2. Nature 2020;581:221-4.
42. Zhang H, Penninger JM, Li Y. Angiotensin-converting enzyme 2 (ACE2) as a SARS- CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46:586–90.
43 Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens 2020;38:781–2.
44. Zou X, Chen K, Zou J. Single- cell RNA- seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019- nCoV infection. Front Med 2020. doi:10.1007/s11684-020-0754-0.
45. Yao XH, Li TY, He ZC. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi 2020;49:E009.
46. Prabhu SD. Cytokine- induced modulation of cardiac function. Circ Res 2004;95:1140–53.
47. Levi M, van der Poll T, Büller HR. Bidirectional relation between inflammation and coagulation. Circulation 2004;109:2698–704.
48. Ding Y, Wang H, Shen H. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003;200:282–9.
49. Farcas GA, Poutanen SM, Mazzulli T. Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus. J Infect Dis 2005;191:193–7.
50. Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr 2020;14:247-50.
51. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl). 2020;133(9):1025–31. https ://doi.org/10.1097/CM9.00000 00000 00074 4.
52. Aghagoli G, Marin BG, Soliman LB, Sellke FW. Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. Journal of Cardiac Surgery 2020;35:1302 – 5.
53. Xu H, Hou K, Xu R, Li Z, Fu H, Wen L, et al. Clinical Characteristics and Risk Factors of Cardiac Involvement in COVID-19. Journal of the American Heart Association 2020;18: https://doi.org/10.1161/JAHA.120.016807.
54. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M. Cardiovascular manifestations and treatment considerations in COVID-19. Heart 2020;106:1132–41.
55. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
56. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID-19 in critically ill patients in the Seattle region: case series. N Engl J Med 2020;382:2012–22.
57. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-segment elevation in patients with COVID-19: a case series. N Engl J Med 2020. Doi:10.1056/NEJMc2009020.
58. Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, et al. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from the

ACC's Interventional Council and SCAI. J Am Coll Cardiol 2020;75:2372–5.
59. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020. Doi:10.1016/j.jacc.2020.04.031.
60. Madjid M, Casscells SW. Of birds and men: cardiologists' role in influenza pandemics. Lancet 2004;364:1309.
61. Madjid M, Aboshady I, Awan I, Litovsky S, Casscells SW. Influenza and cardiovascular disease: is there a causal relationship? Tex Heart Inst J 2004;31:4–13.
62. Vardeny O, Solomon SD. Influenza vaccination: a one-shot deal to reduce cardiovascular events. Eur Heart J 2017;38:334–7.
63. Wang EY, Hulme OL, Khurshid S, Weng LC, Choi SH, Walkey AJ, et al. Initial precipitants and recurrence of atrial fibrillation. Circ Arrhythm Electrophysiol 2020;13:e007716.
64. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020;22:911–5.
65. Bandyopadhyay D, Ashish K, Ghosh S, Hajra A, Modi VA. Cardiovascular implications of Zika virus infection. Eur J Intern Med. 2018;52:e35–e3636.
66. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GW, et al. Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J. 2006;82(964):140–4.
67. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531-8.
68. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with Coronavirus Disease 2019 (COVID-19): possible mechanisms. J Card Fail. 2020. https ://doi.org/10.1016/j.cardfail.2020.04.009.
69. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020. https :// doi.org/10.1016/j.ajem.2020.04.048.
70. Rivara MB, Bajwa EK, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Prognostic significance of elevated cardiac troponin-T levels in acute respiratory distress syndrome patients. PLoS ONE. 2012;7(7):e40515.
71. Bajwa EK, Boyce PD, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Biomarker evidence of myocardial cell injury is associated with mortality in acute respiratory distress syndrome. Crit Care Med. 2007;35(11):2484–90.
72. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5):2000524.
73. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol. 2020. https ://doi.org/10.1002/jmv.25809.
74. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116–21.
75. Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. J Infect. 2020. https ://doi.org/10.1016/j.jinf.2020.03.021.
76. Li JW, Han TW, Woodward M, Anderson CS, Zhou H, Chen YD, et al. The impact of novel coronavirus on heart injury: a systematic review and meta-analysis. Prog Cardiovasc Dis. 2020. https ://doi.org/10.1016/j.pcad.2020.04.008.
77. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovasc Dis. 2020. https ://doi. org/10.1016/j.pcad.2020.03.001.
78. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection. 2020. https ://doi.org/10.1007/ s1501 0-020-01424 -5.
79. Hua A, O'Gallagher K, Sado D, Byrne J. Life-threatening cardiac tamponade complicating

myo-pericarditis in COVID-19. Eur Heart J. 2020. https ://doi.org/10.1093/eurhe artj/ehaa253.
80. Meyer P, Degrauwe S, Van Delden C, Ghadri JR, Templin C. Typical Takotsubo syndrome triggered by SARS-CoV-2 infection. Eur Heart J. 2020;41(19):1860.
81. Minhas AS, Scheel P, Garibaldi B, Liu G, Horton M, Jennings M, et al. Takotsubo Syndrome in the Setting of COVID-19 Infection. JACC Case Rep. 2020. https :// doi.org/10.1016/j.jaccas.2020.04.023.
82. Harikrishnan S, Mohanan PP, Chopra VK, Ambuj R, Sanjay G, Manish B, et al. Cardiological society of India position statement on COVID-19 and heart failure. Indian Heart J. 2020. https ://doi.org/10.1016/j.ihj.2020.04.012.
83. Tam CF, Cheung KS, Lam S, Wong A, Yung A, Sze M, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST Segment-Elevation Myocardial Infarction Care in Hong Kong, China. Circ Cardiovasc Qual Outcomes. 2020;13(4):e006631.
84. Park J, Choi KH, Lee JM, Kim HK, Hwang D, Rhee TM, et al. Prognostic implications of door-to-balloon time and onset-to-door time on mortality in patients with ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Heart Assoc. 2019;8(9):e012188.
85. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362.
86. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9.
87. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in Intensive Care Unit. A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020. https ://doi.org/10.1111/jth.14850.
88. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020. https ://doi.org/10.1016/j.thromres.2020.04.013.
89. Rotzinger DC, Beigelman-Aubry C, von Garnier C, Qanadli SD. Pulmonary embolism in patients with COVID-19: Time to change the paradigm of computed tomography. Thromb Res. 2020;190:58–9.
90. Casey K, Iteen A, Nicolini R, Auten J. COVID-19 pneumonia with hemoptysis: acute segmental pulmonary emboli associated with novel coronavirus infection. Am J Emerg Med. 2020. https ://doi.org/10.1016/j.ajem.2020.04.011.
91. Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp Clin Cardiol. 2013;18(2):129.
92. Kollias A, Kyriakoulis KG, Dimakakos E, Poulakou G, Stergiou GS, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020. https ://doi.org/10.1111/bjh.16727.
93. Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: a comment. J Thromb Haemost. 2020.
94. Thachil J. The versatile heparin in COVID-19. J Thromb Haemost. 2020. https ://doi.org/10.1111/jth.14860.
95. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J Thromb Haemost. 2020. https ://doi. org/10.1111/jth.14828.
96. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. DOACs and 'newer' haemophilia therapies in COVID-19. J Thromb Haemost. 2020. https ://doi.org/10.1111/jth.14841.
97. Asakura H, Ogawa H. Potential of heparin and nafamostat combination therapy for COVID-19. J Thromb Haemost. 2020. https

://doi.org/10.1111/jth.14858.
98. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020. https ://doi.org/10.1111/jth.14869.
99. Paranjpe I, Fuster V, Lala A, Russak A, Glicksberg BS, Levin MA, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020. https ://doi.org/10.1016/j.jacc.2020.05.001].
100. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5. https ://doi.org/10.1016/j.ijid.2020.03.017.
101. Jia X, Yin C, Lu S, Chen Y, Liu Q, Bai J, et al. Two things about COVID-19 might need attention. Preprints. 2020. https ://doi. org/10.20944 /prepr ints2 02002 .0315.v1.
102. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension. 2020;75(6):1382–5.
103. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020. https ://doi.org/10.1161/CIRCR ESAHA .120.31713 4.
104. Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB, Harrington DP. Inhibitors of the renin–angiotensin–aldosterone system and Covid-19. N Engl J Med. 2020. https ://doi.org/10.1056/ NEJMe 20129 24.
105. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol. 2020. https ://doi.org/10.1001/jamac ardio .2020.1624.
106. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc. 2020;9(7):e016219.
107. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and antihypertensives (angiotensin receptor blockers and angiotensin-converting enzyme inhibitors) in coronavirus disease 2019. Mayo Clin Proc. 2020. https ://doi.org/10.1016/j.mayoc p.2020.03.026.
108. Hajra A, Bandyopadhyay D. COVID-19 and ACEI/ARB: not associated? Am J Hypertens. 2020. https ://doi.org/10.1093/ajh/ hpaa0 76.
109. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;323(18):1824–36.
110. US FDA. Kaletra prescribing information. https ://www.acces sdata .fda.gov/drugs atfda _docs/label /2013/02125 1s046 _021906s039 lbl.pdf. Accessed 18 May 2020.
111. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med Infect Dis. 2020;34:101615.
112. Dabbagh MF, D'Souza P, Weinmann AJ, Bhargava P, Basir MB. Cardiac Tamponade Secondary to COVID-19. JACC Case Rep. 2020. https ://doi.org/10.1016/j.jacca s.2020.04.009.