Cardiovascular and Cerebrovascular Complications With COVID-19

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Abstract: The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 has affected the health of people across the globe. Cardiovascular diseases (CVDs) have a significant relationship with COVID-19, both as a risk factor and prognostic indicator, and as a complication of the disease itself. In addition to predisposing to CVD complications, the ongoing pandemic has severely affected the delivery of timely and appropriate care for cardiovascular conditions resulting in increased mortality. The etiology behind the cardiac injury associated with severe acute respiratory syndrome coronavirus-2 is likely varied, including coronary artery disease, microvascular thrombosis, myocarditis, and stress cardiomyopathy. Further large-scale investigations are needed to better determine the underlying mechanism of myocardial infarction and other cardiac injury in COVID-19 patients and to determine the incidence of each type of cardiac injury in this patient population. Telemedicine and remote monitoring technologies can play an important role in optimizing outcomes in patients with established CVD. In this article, we summarize the various impacts that COVID-19 has on the cardiovascular system, including myocardial infarction, myocarditis, stress cardiomyopathy, thrombosis, and stroke.

Key Words: COVID-19, cardiovascular disease, myocardial infarction, thrombosis, myocarditis, Takotsubo cardiomyopathy

In December 2019, a cluster of pneumonia cases caused by a novel coronavirus, now named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began to spread around the Hubei Province of China. The virus, which causes the clinical condition known as the coronavirus disease 2019 (COVID-19), quickly spreads, and by March 11, 2020, the World Health Organization declared COVID-19 as a pandemic. As of January 26, 2021, the SARS-CoV-2 virus has infected 100,243,101 people worldwide and has been responsible for the deaths of 2,156,850. For comparison, the overall COVID-19 case fatality rate is estimated at around 2–3%. In addition, patients with preexisting CVD had a higher in case fatality rate of 10.5%. For comparison, the overall COVID-19 case fatality rate is estimated at around 2–3%. In addition, patients with preexisting CVD were more likely to require admission to an intensive care unit (ICU). A study of 607 consecutive hospitalized COVID-19 patients in Turkey indicated that 150 presented with concomitant cardiac injury. In addition to the higher mortality rate and increased risk of requiring ICU level care, these patients with cardiac injury were more likely to have longer hospital stays and had a higher risk of developing acute kidney injury and acute respiratory distress syndrome.

In a study of 132,312 patients with established heart failure and hospitalized between April 1, 2020, to September 30, 2020, 8383 patients (6.4%) were hospitalized with COVID-19, and 100,068 patients (75.6%) were hospitalized with nonacute heart failure reasons. Hospitalization with COVID-19 was associated with greater inhospital mortality risk (24.2%) compared with hospitalization with acute heart failure (2.6%). Among patients with heart failure hospitalized with COVID-19, higher age, male sex, and morbid obesity were associated with greater odds of inhospital mortality.

Data from several studies indicated that age, diabetes mellitus, hypertension, and coronary artery disease history were independent predictors of inhospital mortality; however, it is uncertain due to the lack of more large-scale studies, whether this association between CVD and COVID-19 prognosis is truly due to causation or correlation, since age is the strongest risk factor for CVD and may also be a risk factor for COVID-19 severity due to immune system function decline. In the same vein, certain CVD risk factors including diabetes and hyperlipidemia have been shown to affect immune system function and therefore may serve as confounding variables to indirectly worsen prognosis and severity of COVID-19.
et al.17 revealed a 7–8% rate of MI in hospitalized patients with pneumonia severity, as well as a complication of the disease itself, the myocardial infarction (MI) rate being 8–12% of patients but that this correlated with disease severity as the 99th percentile of the upper reference limit was only found in one-third of the patients, type 2 MI, due to an acute oxygen supply and demand mismatch from a cause other than coronary artery disease, could not be ruled out. It is unknown whether these patient presentations were due to SARS-CoV-2 induced myocarditis, endothelial dysfunction, or cytokine storm.18

In another study, 18 patients with confirmed COVID-19 across six New York hospitals presented with ST-segment elevation. Out of the patients who received angiography, 33.3% did not have any obstructive disease, once again ruling out type 1 MI in a large percentage of patients. Similarly, the underlying mechanism behind these presentations is unclear, but may include coronary spasm, microthrombi, endothelial injury, cytokine storm, or plaque rupture, among other hypotheses.20 There are also reports of increased risk for stent thrombosis in patients with COVID-19. A case series described four cases of stent thrombosis, one acute in the setting of an STEMI and three very late, which the authors attributed to infection with SARS-CoV-2.21 In a postmortem pathologic study of 40 hearts of COVID-19 infected patients, 14 (35%) had evidence of myocyte necrosis, predominantly of the left ventricle, of whom three (21%) showed evidence of acute MI.22 Cardiac thrombi were present in 11/14 (78.6%) cases with necrosis, with 2/14 (14.2%) having epicardial coronary artery thrombi, whereas 9/14 (64.3%) had microthrombi in myocardial capillaries, arterioles, and small muscular arteries. The authors noted that the microthrombi from COVID-19 patients had significantly greater fibrin and terminal complement C5b-9 immunostaining as compared with intramyocardial thromboemboli from COVID-19 negative subjects and to aspirated thrombi.23

At Westchester Medical Center in Valhalla, New York, the number of STEMI patients during the local peak of the COVID-19 pandemic was compared with the number of STEMI patients during the same time of the year prior. Between March and May of 2019, 17 patients presented to Westchester Medical Center with STEMI, whereas 23 STEMI patients presented between March and May of 2020. It is uncertain, however, whether this 35% increase in STEMI patients was directly caused by COVID-19. Of the 23 patients who presented with STEMI in March–May of 2020, two patients were confirmed to be positive for COVID-19; both of these patients presented in May. Unfortunately, during the height of the COVID-19 pandemic in New York, especially in March and April, COVID-19 testing was extremality limited; therefore, it is impossible to know how many of those 21 remaining STEMI patients were in fact positive for the disease.

**CORONARY AND EXTRACORONARY THROMBOSIS**

Research has shown that COVID-19 infection predisposes to hypercoagulability and a propensity to clot in many patients.24 Excessive inflammation triggered by the cytokine storm, the massive macrophages, and platelet activation and endothelial dysfunction could be associated with the development of coagulopathy.25 Immune-mediated thrombotic mechanisms, complement activation, macrophage activation syndrome, antiphospholipid antibody syndrome, hyperferritinemia, and renin-angiotensin system dysregulation have been postulated to increase thrombotic risk.24 Patients in the ICU with severe COVID-19 have demonstrated a particularly high incidence of
thrombotic complications of around 31%.26 Although the mechanism behind this hypercoagulable state is still underdetermined at the present time, thrombotic complications have significantly contributed to morbidity and mortality associated with SARS-CoV-2 infection.14

Despite the previously discussed studies that revealed high rates of nonobstructed coronary arteries on angiography, others have found large amounts of thrombosis and multivessel obstructions. One study followed 115 patients admitted with STEMI, who each underwent angiography. Images were then reviewed by three interventional cardiologists who were blinded to the patients’ COVID-19 status.27 The SARS-CoV-2-positive patients were more likely to have additional cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, and previous history of percutaneous coronary intervention (PCI). Furthermore, the SARS-CoV-2-positive patients had higher levels of high sensitivity troponin, D-dimer, and C-reactive protein, as well as lower lymphocyte counts. There was a significantly higher incidence of multivessel disease in this positive patient population ($P = 0.0003$) and higher incidence of cardiac arrest (28% vs 9%). Not only was multivessel thrombosis significantly higher in the positive group, but also the rate of in-stent thrombosis post-intervention was significantly higher as well ($P = 0.04$), supporting the role of COVID-19 as a risk factor for thrombotic events (Fig. 1). All of the COVID-19-positive patients in this cohort presented with STEMI as their first manifestation of disease. Therefore, the presence of an ST-STEMI may itself be considered a thrombotic complication of SARS-CoV-2 infection.

This highlights the importance of recognizing a patient’s COVID-19 status, as it has the potential to change their management and course of treatment. A study spanning four hospitals across Italy, Lithuania, Spain, and Iraq between February 1, 2020, and April 15, 2020, also showed high levels of in-stent thrombosis within SARS-CoV-2 patients. Among this group of patients, those treated with PCI had an in-stent thrombosis rate of 21%—a stark contrast from previous rates of around 1%.28 However, a study in Poland found no significant difference of PCI outcomes in COVID-19-positive and COVID-19-negative patients.29 Although further studies are needed to determine the true impact of COVID-19 on PCI outcomes, the use of anticoagulation may have the ability to decrease COVID-19 complications and improve patient outcomes.28

In addition to the large vessel thrombosis observed in the SARS-CoV-2-positive patient population, there has also been evidence of microvascular thrombotic disease that may be contributing to cardiovascular complications. A case report of a woman with COVID-19 and ST-segment elevations in the inferior and lateral leads revealed histological evidence of microthrombi. Postmortem analysis exposed small vessels with platelet and fibrin thrombi, along with areas of patchy myocardial necrosis, inflammation, and hemorrhage.33 This suggests that the microvascular thrombotic disease served as the underlying mechanism behind the patient’s MI. Microvascular thrombosis may therefore be a source of MI in COVID-19 patients even without the presence of epicardial coronary artery obstruction.31

In addition to coronary thromboses, COVID-19 infection is associated with increased risk for arterial and venous thromboembolism (VTE). Tinelli et al23 reported a case of complete aortic thrombosis in a patients with COVID-19 who presented in cardiogenic shock leading to death. Estimates for VTE varied between studies and pulmonary embolism, and deep vein thrombosis were the most frequently noted thrombotic events in COVID-19, with initial reports noting an incidence of 20–30% in critically ill patients.24 The increased risk was noted despite universal thromboprophylaxis, and the risk of all cause death in that cohort was fivefold higher among patients with a thrombotic event (hazard ratio, 5.4; 95% confidence interval [CI], 2.4–12).24 In another study of 9407 patients with COVID-19 infection, the overall VTE rate was 2.9% (2.4% in the medical ward and 4.9% in the ICU) and a VTE or mortality rate of 26.1%.30 In a recent study of 3239 patients with COVID-19, the overall VTE rate was 6.3%.31

D-dimer, thrombocytopenia, and interleukin-6 are promising markers of COVID-19 severity and could be considered in the laboratory testing to assess thrombotic risk.32 COVID-19-infected patients, whether hospitalized or ambulatory, are at high risk for VTE, and an early and prolonged pharmacological thromboprophylaxis with low-molecular-weight heparin is highly recommended.33 A recent retrospective study in 3239 patients analyzed the role of early therapeutic anticoagulation on mortality and noted that among critically ill adults with COVID-19, early therapeutic anticoagulation did not affect survival.31 Randomized trials are urgently needed to determine the safety of proposed therapeutic anticoagulation with heparin and the role for antithrombotic agents in patient management.32

**Myocarditis**

Myocarditis is an uncommon diagnosis occurring in 4.5–7.2% of highly selected cases undergoing autopsy or endomyocardial biopsy.34,35 Available data suggest that myocarditis as a cause of myocardial injury in patients with COVID-19 is uncertain and rates of fatal myocarditis are low. Although an inflammatory response to COVID-19 infection could be reported in cases with higher myocardial virus load versus no virus infection, this was not associated with an influx of no inflammatory cell infiltrates or differences in leukocyte numbers.36

ST-segment elevations, while typically manifested in STEMI, can also be present in myocarditis—an inflammatory disease of the myocardium that is another potential complication of SARS-CoV-2 infection. A meta-summary of COVID-19 patients with suspected myocarditis revealed that 25% of the confirmed myocarditis cases had ST-segment changes including elevation and depression.37 Many symptoms of myocarditis overlap with acute coronary syndrome such as chest pain, fatigue, and dyspnea; however, on angiography, myocarditis does not produce an obstruction of the coronary arteries. There is also significant overlap in symptoms of primary COVID-19 and suspected myocarditis in COVID-19 patients.38

Stable patients with COVID-19 or other recent viral infections, who present with acute chest pain and normal angiography, could undergo further workup including echocardiography and cardiovascular magnetic resonance (CMR) imaging using the Lake Louise criteria, which has a specificity of up to 91% for detecting myocarditis.39 CMR can aid in differentiating myocarditis from non-obstructive type 2 MI or stress cardiomyopathy.40 When CMR imaging is not feasible, cardiac computed tomographic (CT) angiography with delayed myocardial imaging may serve to exclude significant coronary artery disease and identify myocardial inflammatory patterns.41 An accurate diagnosis is significant, as myocarditis in COVID-19 patients have the potential for rapid clinical deterioration and warrant a multidisciplinary treatment approach.42 CMR analysis of 145 competitive student athletes recovering from mostly mild COVID-19 demonstrated a low prevalence of myocarditis (1.4%) and the authors questioned the utility of CMR as a screening tool for myocarditis in this patient population. However, this is a relatively low risk population with only predominantly mild COVID-19 (50% cases), so these findings might not be generalizable. Recommendations regarding endomyocardial biopsy are not consistent across recommendations.34,40 However, given its extremely low frequency and unclear therapeutic implications, the routine use of endomyocardial biopsy to diagnose myocarditis in the setting of COVID-19 might not be entirely beneficial.34
Several case reports have also demonstrated instances of Takotsubo cardiomyopathy in COVID-19-positive patients. \(^4^1\), \(^4^2\) Takotsubo cardiomyopathy is a syndrome that is typically triggered by emotional distress but has also been associated with respiratory failure and infections. It is characterized by acute and transient regional left ventricular systolic dysfunction. \(^4^1\) There was a significant increase in the incidence of stress cardiomyopathy during the COVID-19 pandemic. \(^4^3\)

**FIGURE 1.** Representation of the possible mechanisms of acute myocardial injury related to COVID-19. A, Myocarditis. B, Type 2 MI (left) and type 1 MI (right). C, Contraction bands in stress cardiomyopathy. D, Microvascular dysfunction from microthrombi and endothelial injury. E, Cytopathic injury in cytokine storm. Reproduced with permission from Lang JP, Wang X, Moura FA, et al. A current review of COVID-19 for the cardiovascular specialist. *Am Heart J*. 2020;226:29–44. Copyright Elsevier. COVID-19 indicates coronavirus disease 2019; CVD, cardiovascular disease; MI, myocardial infarction.
COVID-19 period, with an incidence proportion of 7.8% compared with prepandemic incidence proportion range of 1.5–1.8% (rate ratio, 4.58; 95% CI, 4.11–5.11; P < 0.001).46

One case report discussed a woman who presented with acute respiratory failure and ECG changes congruent with STEMI; however, her echocardiogram results were classic for Takotsubo cardiomyopathy with mid-distal left ventricular hypokinesis and apical ballooning. Another reported a woman who had negative T waves and repolarization phase alternations on ECG, but similarly, the echo showed apical ballooning and hypokinesis of the mid-ventricular segments.

An additional study looked at COVID-19 patients at The Mount Sinai Hospital in New York who underwent clinically indicated transthoracic echocardiogram. Out of 118 consecutive patients, five of them (4.2%) had features compatible with Takotsubo cardiomyopathy. On their ECG taken most closely to the echo, two out those five patients had ST-segment elevations as well. These patients were also shown to have higher peak levels of troponin I and creatinine kinase-MB. Takotsubo cardiomyopathy is another form of cardiac injury that should be considered in a differential diagnosis in COVID-19 patients.43

CEREBROVASCULAR DISEASE

Stroke is an important complication of COVID-19. Acute ischemic stroke, particularly of the cryptogenic type, is the predominant form. Ischemic stroke was reported as a complication on certain viral syndromes (0.7%), but the incidence is higher with SARS-CoV-2 infection (1.6%).47 Inflammation both local and systemic, endothelial injury, and hypercoagulability associated thrombosis were implicated in the pathogenesis of ischemic stroke in COVID-19 patients.48 Multicenter studies and meta-analysis reported a 0.5–4.5% incidence of stroke in patients with COVID-19, depending on the patient demographic studied.49–51 The higher the severity of COVID-19, the higher the risk of acute stroke.

In a recently published large cohort analysis of 67,845 patients with SARS-CoV-2, 1.3% were hospitalized for cerebrovascular events, 1.1% for ischemic stroke, and 0.2 for hemorrhagic stroke. Compared with noninfected contemporary or historical controls, patients with SARS-CoV-2 infection had increased odds of ischemic stroke (odds ratio [OR] = 3.58; 95% CI = 1.43–8.92) and cryptogenic stroke (OR = 3.98; 95% CI = 1.62–9.77).52 SARS-CoV-2 infection status was not associated with the likelihood of receiving intravenous thrombolysis among hospitalized ischemic stroke patients during the COVID-19 pandemic. Odds of inhospital mortality were higher among SARS-CoV-2 stroke patients than noninfected contemporary or historical stroke patients (OR = 5.60, 95% CI = 3.19–9.80). In a review of neuroimaging findings from 954 patients with COVID-19 and associated neurological manifestations, ischemia with large vessel occlusion event was revealed in 59.9% of ischemic stroke patients, whereas 69.2% of patients with intracerebral hemorrhage exhibited bleeding in a location that was not associated with hypertension. Calsallosal and/or juxtaocular location was identified in 58.7% of cerebral microbleed positive images.50 In another study, the authors suggested a possibly higher proportion of microangiopathic involvement or undetected distal large-vessel occlusion with COVID-19-related strokes.

In an analysis of 277 patients with stroke of whom 105 (38%) had COVID-19, COVID-19-positive patients were more likely to have a cryptogenic (51.8% vs 22.3%, P < 0.0001) stroke cause and were more likely to suffer ischemic stroke in the temporal (P = 0.02), parietal (P = 0.002), occipital (P = 0.002), and cerebellar (P = 0.028) regions. Outcomes were worse among COVID-19-positive patients, including longer length of stay (P < 0.0001), greater percentage requiring ICU care (P = 0.017), and greater rate of neurological worsening during admission (P < 0.0001); additionally, more COVID-19-positive patients suffered inhospital death (33% vs 12.9%, P < 0.0001).52 In a study of 550 acute stroke patients from seven centers in Spain, 124 (22.6%) had COVID-19. There were no differences found in the rates of reperfusion therapies in ischemic strokes (45.5% non-COVID-19, 35.7% confirmed COVID-19, and 40% suspected COVID-19; P = 0.265). However, the COVID-19 group had longer median door-to-puncture time (110 vs 80 minutes) due to performance of chest CT imaging. Multivariate analysis confirmed poorer outcomes for confirmed or suspected COVID-19 (adjusted ORs, 2.05 [95% CI, 1.12–3.76] and 3.56 [95% CI, 1.15–11.05], respectively). COVID-19 has more severe strokes and poorer outcomes despite similar acute management.53

In addition to increasing stroke risk, the COVID-19 pandemic has also caused disruptions in optimal stroke care delivery and decreased stroke hospitalizations resulting in poor outcomes.54,55 A “hospital avoidance” nature was noted among stroke patients due to the pandemic restrictions and the fear of being exposed to infected individuals at medical centers.56 A meta-analysis on nine studies with 59,233 subjects showed that the number of stroke alerts, reperusions, and mechanical thrombectomies was reduced by 36%, 31%, and 22%, respectively, during the pandemic. However, the number of patients receiving mechanical thrombectomy per stroke increased by 23%, which could probably result from a higher admission threshold for stroke during the pandemic and decreased admission rates for milder strokes.57,58 These findings were confirmed in other larger studies in which the authors reported that reperfusion treatments declined by 31% and specifically thrombolysis by 33% during the pandemic.59 Data from several large stroke centers have demonstrated that compared with patients in the prepandemic, patients with acute ischemic stroke during the pandemic had three times the discharge mortality despite having statistically similar rates of door to head CT time to groin puncture times, time to alteplase administration, door to reperfusion times, and successful recanalization.60 These findings are concerning, and while we investigate the optimal strategies to identify and manage acute stroke in patients with COVID-19, we should have pathways to maintain availability of stroke care during the COVID-19 outbreak as these are crucial to prevent indirect mortality and disability due to suboptimal care, while decreasing potential COVID-19 exposure to patients and healthcare providers.51,62 Telemedicine and telestroke assessments have an important role to play in these pathways.61 A well-established stroke care network helps to diminish the impact of such an outbreak in stroke care, reducing secondary transfers and allowing maintenance of reperfusion therapies, with a minor impact on door-to-puncture times, which were longer in patients who underwent chest computed tomography.64

SUMMARY AND FUTURE DIRECTIONS

CVD is common in severe COVID-19 presentations both as a predisposing risk factor and as complications. Patients with preexisting CVD have worse outcomes with COVID-19 and patients with heart failure hospitalized with COVID-19 are at high risk for complications, with nearly one in four dying during the hospitalization. In addition to predisposing to CVD complications, the ongoing pandemic has severely affected the delivery of timely and appropriate care for cardiovascular conditions resulting in increased mortality.8,9 Cardiac injury and specifically increased troponin levels have been shown to lead to worse clinical outcomes and higher mortality rates. Children with multisystem inflammatory syndrome from SARS-CoV-2 infection have several cardiac manifestations common, including ventricular dysfunction, coronary artery dilation and aneurysms, arrhythmia, and conduction abnormalities.64 The etiology behind the cardiac injury associated with SARS-CoV-2 is likely varied, including coronary artery disease, microvascular thrombosis, myocarditis, and even stress cardiomyopathy. Furthermore, large-scale investigations...
are needed to better determine the underlying mechanism of MI and other cardiac injury in COVID-19 patients, and to determine the incidence of each type of cardiac injury in this patient population. Determining the etiology of cardiac injury is imperative, as it can change the clinical management of the patient and also potentially provide further information about how to prevent these cardiac injuries in future COVID-19 patients and improve outcomes. Telemedicine and remote monitoring technologies can play an important role in optimizing outcomes in patients with established CVD.

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