EDITORIAL

Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality

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Coronavirus disease 2019 (COVID-19) has emerged as a pandemic and a public health crisis of global proportions. As a medical community, we are actively engaged in a real-time data gathering mode to facilitate active learning and an expedited study of best practices of care. Although we are becoming more aware of the natural history of COVID-19, we have had scant information as of yet that addresses any unique risks of COVID-19 for those with underlying cardiovascular disease. Such information is of paramount importance as we now must begin to consider the potential for direct and indirect adverse effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the heart and especially so in those with already established heart disease.

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The statistics to date are staggering and relentlessly mounting. As of March 25, 2020, there have been more than 430 000 individuals in more than 170 countries with confirmed COVID-19, of whom more than 19 000 have died. In the US, there have been more than 49 000 confirmed cases of COVID-19 in all 50 states and Washington, DC. It is clear that the number of infections in the US, the number needing critical care interventions, and especially the numbers of deaths will continue to escalate.

The available data from China and Italy as well as the early experience in the US indicate that COVID-19 is a relatively mild condition in most affected individuals, but in others, it can be very severe and deadly. What we now know is that individuals at greatest risk of serious illness sufficient to require intensive care and those at greatest risk of mortality are older individuals, particularly older individuals with underlying comorbid disease, including cardiovascular disease.[1-5] However, severe disease requiring hospitalization and even deaths have been reported in younger adults.

Patients with long-term coronary artery disease and those with risk factors for atherosclerotic cardiovascular disease have a heightened risk of developing an acute coronary syndrome during acute infections, which has been shown previously in epidemiologic and clinical studies of influenza[6-8] and other acute inflammatory conditions.[9] Such acute coronary events could result from the severe increase in myocardial demand triggered by infections that precipitate myocardial injury or infarction, akin to type 2 myocardial infarction. Alternatively, circulating cytokines released during a severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture. Similarly, patients with heart failure are also prone to hemodynamic decompensation during the stress of severe infectious illnesses. Thus, it is anticipated that patients with underlying cardiovascular diseases, which are more prevalent in older adults, would be susceptible to higher risks of adverse outcomes and death during the severe and aggressive inflammatory responses to COVID-19 than individuals who are younger and healthier. In addition, acute/fulminant myocarditis as well as heart failure have been reported with Middle East respiratory syndrome coronavirus and could be expected to occur with SARS-CoV-2, given the similar pathogenicity.

Two articles published in *JAMA Cardiology* from 2 academic hospitals in Wuhan, China, the epicenter of the COVID-19 pandemic,[10,11] support these concepts while also providing novel insights into the incidence and consequences of myocardial injury associated with SARS-CoV-2. Shi et al[10] present a cohort study of 416 hospitalized patients with COVID-19 confirmed by reverse transcriptase–polymerase chain reaction, of whom 82 (19.7%) had evidence of myocardial injury manifested by elevation of high-sensitivity troponin I (TnI) levels. Patients with myocardial injury had a significantly higher in-hospital mortality rate (42 of 82 [51.2%]) compared with those without myocardial injury (15 of 335 [4.5%]), and among those with myocardial injury, greater degrees of TnI elevation were associated with higher mortality rates.

Similar observations were reported by Guo et al[11] in 187 patients hospitalized with laboratory-confirmed COVID-19, of whom 52 (27.8%) had myocardial injury as determined by elevated levels of troponin T (TnT). In-hospital mortality was 59.6% (31 of 52) in those with elevated TnT levels compared with 8.9% (12 of 135) in those with normal TnT levels. Of note, the highest mortality rates were observed in those with elevated TnT levels who had underlying cardiovascular disease (25 of 36 [69.4%]), but mortality rates were also considerable in those with elevated TnT levels without prior cardiovascular disease (6 of 16 [37.5%]). In contrast, patients with known cardiovascular disease without elevation of TnT levels had a relatively favorable but still worrisome prognosis (mortality of 13.3% [4 of 30]). Guo et al[11] provide additional novel insights that TnT levels are significantly associated with levels of C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP), thus linking myocardial injury to severity of inflammation and ventricular dysfunction. Their data also show progressive serial increases in both TnT and NT-proBNP levels during hospitalization in patients who follow a deteriorating clinical course toward death, whereas those with a more favorable outcome with less severe illness, successful

treatment, and hospital discharge show stable low levels of these biomarkers.

Shi et al[10] and Guo et al[11] report remarkably similar characteristics of patients who develop myocardial injury (as assessed by elevated levels of TnI or TnT) associated with COVID-19. Patients at risk of myocardial injury are older and have a higher prevalence of hypertension, coronary artery disease, heart failure, and diabetes than those with normal levels of TnI or TnT. Patients with myocardial injury also have evidence of more severe systemic inflammation, including greater leukocyte counts and higher levels of C-reactive protein and procalcitonin as well as high levels of other biomarkers of myocardial injury and stress, such as elevated creatine kinase, myoglobin, and NT-proBNP. Further, patients who develop myocardial injury with COVID-19 have clinical evidence of higher acuity, with a higher incidence of acute respiratory distress syndrome and more frequent need for assisted ventilation than those without myocardial injury. Thus, a consistent picture emerges from these 2 reports that older patients with preexisting cardiovascular comorbidities and diabetes are prone to develop a higher acuity of illness after contracting SARS-CoV-2 associated with higher risk of myocardial injury and a markedly higher short-term mortality rate.[10,11]

These lines of evidence are followed by Yang and Zin[12] in their Viewpoint that discusses the collision between the acute COVID-19 epidemic that has arisen in the past 3 months and the underlying cardiovascular epidemic that has been under way in China for decades. They acknowledge the many recent observations[1-5] that patients with preexisting cardiovascular disease are susceptible to the most adverse complications of COVID-19, including death. Importantly, they also appropriately emphasize that there has thus far been insufficient attention to understanding the mechanisms responsible for these outcomes beyond the obvious recognition that severe infections can destabilize patients with coronary artery disease or heart failure. The current observations of Shi et al[10] and Guo et al[11] regarding the important association of myocardial injury with adverse outcomes begin to provide insights into other possible mechanisms, including demand ischemia that devolves into myocardial injury or plaque disruption stimulated by intense systemic inflammatory stimuli. As with other coronaviruses, SARS-CoV-2 can elicit the intense release of multiple cytokines and chemokines[1,12] that can lead not only to vascular inflammation and plaque instability but also to myocardial inflammation. Direct viral infection of the myocardium is another possible causal pathway of myocardial damage and one that requires further investigation. It is noteworthy that the articles from China by Shi et al,[10] Guo et al,[11] and Yang and Zin[12] address the unique marked affinity of SARS-CoV-2 for the host angiotensin-converting enzyme 2 receptor, which has been shown previously for other coronaviruses,[13] raising the possibility of direct viral infection of vascular endothelium and myocardium. It is thus possible that in some patients with or without preexisting cardiovascular disease, COVID-19–associated myocardial injury could represent myocarditis.[14] The well-documented case of acute myocarditis following a COVID-19–associated respiratory infection in a 53-year-old Italian woman with no previous heart disease, also reported in this issue by Inciardi et al,[15] supports this hypothesis.

The association of myocardial injury with outcomes of COVID-19 in the 2 Chinese cohorts[10,11] represent early data from patients hospitalized at the outset of the epidemic in Wuhan, during which a rapidly escalating number of patients with previously unknown serious respiratory illnesses was beginning to stretch and overwhelm local health care systems. Given the severity of illness and the primary focus on urgently managing infection and respiratory failure, it is understandable that not all patients have complete cardiac data, such as electrocardiography, and that information from more sophisticated cardiac testing, such as echocardiography, coronary angiography, and magnetic resonance imaging, are not available. That we have the current data available to study is in itself a triumph and an acknowledgment of the intent of dedicated physicians to use bedside observations to inform others.

Whether the data linking myocardial injury and high mortality risk in patients with COVID-19 from the 2 Chinese cohorts[10,11] are generalizable to other countries, including the US, is yet to be determined. But the wake-up call has been delivered. We have a similar profile of elderly patients with cardiovascular disease in the US and other Western countries in which the toll of COVID-19 could be daunting. While remarkable efforts to unravel the mechanisms of myocardial injury are ongoing and candidate therapies are already entering clinical trials, as discussed in the comprehensive and scholarly review by Madjid et al,[16] one message resonates with us: prevention. Until we know more, the populations described in these primary data reports should be most observant of strict hand hygiene, social distancing, and, where available, COVID-19 testing.

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