Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Understanding ST-Elevation Myocardial Infarction in COVID-19: The Marriage of Bench Work and Big Data

COVID-19 has led to substantial morbidity and mortality around the world and altered healthcare delivery in nearly every hospital in every country. While COVID-19 infection commonly is thought primarily to affect the pulmonary system, the cardiovascular effects cannot be disregarded.[1-3]

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus responsible for COVID-19. It is the third beta-coronavirus to have caused an infectious outbreak. Each of these epidemics, or pandemics, caused by beta-coronaviruses has involved not only respiratory manifestations in those infected, but also significant effects on the cardiovascular system. The first known beta-coronavirus epidemic was in 2003, when SARS-CoV-1 led to the outbreak of SARS and commonly was noted to cause hypotension and tachycardia.[1] Some patients suffered more severe cardiac manifestations, including arrhythmia, cardiomegaly, diastolic dysfunction, direct damage to the myocardium, vasogenic shock, and unstable coronary plaques. In 2012, the Middle East Respiratory Syndrome (MERS) coronavirus outbreak caused acute myocarditis, myocardial edema, and left ventricular dysfunction in some infected patients.[1] Similar to its beta-coronavirus predecessors, COVID-19 leads to cardiac manifestations; however, the common presentation differs, and the severity is enhanced. With COVID-19, myocardial injury is in the form of ST-elevated myocardial infarction (STEMI) or Non-ST elevated myocardial infarction (NSTEMI) and is the predominant cardiac manifestation, with an estimated incidence of 7.2%-to-27.8% in patients who have COVID-19.[1]

A potential reason for the association of myocardial infarction with COVID may be due to the mechanism in which SARS-CoV-2 enters cells in order to replicate. Both SARS-CoV-1 and SARS-CoV-2 bind to the angiotensin-converting enzyme 2 (ACE2) receptor. However, SARS-CoV-2 has a ten- to 20-fold greater affinity for this receptor compared to SARS-CoV-1.[4] The ACE2 receptor is expressed on many tissues, including the upper airway, which allows for inhalation and droplet entry; the lungs, leading to pulmonary manifestations; and the heart.[4] Not only does SARS-CoV-2 likely lead to direct myocardial injury within myocytes, it also has negative effects on the renin-angiotensin-aldosterone system (RAAS) due to ACE2-receptor binding.

As SARS-CoV-2 binds to the ACE2 receptor, the available number of ACE2 receptors decreases. This is important because the ACE2 receptor is responsible for downregulation of the RAAS system. Although the mechanisms still are being elucidated, it is possible this binding results in unhindered RAAS action, leading to vasoconstriction and aldosterone release, which both could have negative effects on cardiac function.[4] RAAS activation also activates the endothelium to upregulate von Willebrand factor, leading to platelet and complement activation. Activated platelets recruit neutrophils to release neutrophil extracellular traps (NETs), which are webs of chromatin, microbicidal proteins, and oxidant enzymes.[5] Although NETs are meant to contain infections, NETs also can promote excessive inflammation and clotting and have been associated with arterial and venous thrombosis, disseminated intravascular coagulopathy, and vasculitis. Importantly, NETs have been found to be elevated in patients with COVID.[6]

All of these components of unbridled RAAS activation may be among the many etiologies behind the notable incidence of thrombotic complications in patients with COVID-19 infection. Whereas most viruses lead to an inflammatory state, COVID appears to be extremely prothrombotic, 34% of critically ill patients with COVID suffer thrombotic complications despite being on anticoagulant thromboprophylaxis.[7] This large percentage does not include unmeasured microthromboses, including those in the coronary vasculature, that likely are simultaneously occurring.

For patients who do suffer myocardial infarctions, the COVID pandemic presents particular challenges in the diagnosis and management of acute coronary syndrome. The reasons for this are two-fold: (1) difficulty in correct diagnosis due to the overlap of symptoms with COVID and myocardial infarction, especially dyspnea and chest pain, and (2) the immediate need for reorganization and triage of every hospitalized patient

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in order to treat patients with COVID and to mitigate the spread of COVID-19.[8]

Thankfully, many researchers quickly were able to organize collaborations and create large registries and databases aimed at understanding how the pandemic affects the healthcare system and specific patient populations. Several such registries took a granular approach and focused on patients who suffered STEMI. Authors recently have begun to publish initial registry and database findings concerning the implications of the COVID-19 pandemic on the diagnosis, treatment, and outcomes of patients who sustained STEMI. The largest such North American registry was created by three major cardiovascular societies (Society for Cardiovascular Angiography and Interventions, Canadian Association of Interventional Cardiologists, and the American College of Cardiology Interventional Council), which collaborated to establish the North American COVID-19 Myocardial Infarction (NACMI) Registry. The aim was to clarify the effect of the pandemic on the clinical management of acute coronary syndrome.[9]

The NACMI registry is a prospective, investigator-initiated, multicenter observational registry of patients specifically hospitalized with STEMI and who have confirmed or suspected COVID infection. It includes 64 sites, of which 52 are located in the United States and 12 are located in Canada. Initial findings were published for patients admitted between January 1, 2020, to December 6, 2020.[10] In this analysis, demographic characteristics, management strategies, and outcomes of patients in the registry (230 patients with confirmed COVID and 495 patients under investigation) were compared to a control group of STEMI patients without COVID infection treated five years before the pandemic (460 patients) and included in the Midwest STEMI Consortium. Patients were matched on the basis of age and sex in a 2:1 ratio of control (prepandemic) to case-matched NACMI registry patients.

Patients who had a STEMI in the setting of infection with COVID were typically male (71%) and between 56 and 75 years of age. The majority of patients positive for COVID were ethnic minorities (61%). The COVID-positive cohort was more likely to have diabetes, but less likely to have other coronary artery disease risk factors, including dyslipidemia, a history of smoking, previous percutaneous intervention (PCI), or previous myocardial infarction, compared to the control group. Additionally, presentation was more atypical in patients with COVID-positive STEMI, presenting with a higher percentage of dyspnea rather than chest pain. When compared to historic non-COVID controls with STEMI, patients with COVID-positive STEMI were more likely to have pulmonary infiltrates on chest x-ray and more likely to be sicker pre-PCI, as evidenced by higher rates of cardiac arrest and cardiogenic shock.

The primary endpoint of the study were the differences in composite in-hospital death, stroke, recurrent infarction, and unplanned revascularization, which were statistically higher in the COVID-positive group (rate of 36%) compared to the control group (rate of 5%). In-hospital mortality rate of the COVID group was 33%, which was significantly higher than that of the control group (4%). It remains unclear whether patients with COVID-positive STEMI died from pulmonary, cardiovascular, or other etiologies. This is an important distinction, as the reported incidence of death from COVID in patients in the intensive care unit, not considering any other morbidities, is nearly 39%.[11]

Central discussion points of this initial publication concerned the variance in management of patients with COVID-positive STEMI when compared to control patients who suffered STEMI prior to the pandemic. During the pandemic, only 78% underwent angiography (compared to 100% of the control), and when they did receive angiography the door-to-balloon time was prolonged (79 minutes *v* 66 minutes). Interestingly, patients positive for COVID were less likely to receive PCI than control patients (71% *v* 93%). This may have been due to the high rate of no culprit lesions found on angiography in patients with STEMI in the setting of COVID infection (23% *v* 1%). Medical treatment alone was prescribed to 20% of patients with COVID, whereas only 2% of patients with STEMI before the pandemic were prescribed medical management without intervention.

The NACMI registry is just one of the many ongoing registries attempting to provide insight into the management of cardiovascular disease during the COVID-19 pandemic. The differences in these registries highlight potential limitations in the NACMI registry. Recently, Lala et al.[12] examined patients from the five hospitals in the Mt. Sinai Health System in New York. Rather than analyzing the therapy offered for STEMI patients, this study focused on the incidence of increased troponin levels and outcomes in patients hospitalized with COVID-19. The study found that 36% of patients hospitalized with COVID-19 had elevated troponin levels, representing myocardial injury. Furthermore, elevated troponin levels in patients with COVID were associated significantly with higher in-patient mortality.

When compared with the NACMI registry, which included both known and suspected patients with COVID, databases such as the one described by Lala et al., which limit enrollment to only patients with COVID instead of analyzing patients under investigation, offer less confusing results. In addition, comparing patients with acute coronary syndrome who were positive for COVID with contemporaneous patients who were COVID-negative may have benefits. In other words, the NACMI comparison of patients with pre pandemic STEMI-to-pandemic STEMI may lead to confounding findings.

This confounding is due to the possibility that patients with STEMI during the pandemic actually fared differently—even if they were COVID-negative—than patients with a history of STEMI from five years ago. In other words, the North American healthcare system encountered challenges in treating all patients, regardless of COVID status. Thus, patients with STEMI who did not have COVID also had their care affected during the pandemic compared to previous cohorts.[13] Furthermore, the effect of delayed presentation for coronary syndromes during the pandemic likely had an equally negative compounding effect on patients with and without COVID. Hence, the outcome analysis by Garcia et al. would be altered if contemporary patients with non-COVID STEMI also had poor outcomes that could not be attributed to COVID infection, but were unfortunate sequelae of limitations on medical care incurred during the pandemic.

This notion was corroborated by another registry, titled the International Study on Acute Coronary Syndromes (ISACS) STEMI COVID-19 registry, which was created in Europe with similar intentions to the NACMI registry.[14] The ISACS registry is much larger than the NACMI registry, including 6,609 patients versus 1,185 patients, respectively. Unlike the NACMI, the ISACS STEMI registry included only patients with STEMI who underwent interventional treatment with PCI. Another difference is that the ISACS STEMI registry included patients regardless of COVID status. In other words, contemporary non-COVID controls were included in the registry. These key differences allowed for secondary and subanalyses via alternative angles on how the pandemic affected cardiovascular care in patients with STEMI.

Similar to the NACMI registry study, the ISACS STEMI analysis compared patient outcomes utilizing two finite time points: intra- versus prepandemic. Similarly, the ISACS STEMI researchers observed a significantly higher mortality in 2020 as compared with pre pandemic mortality in 2019 (6.8% *v* 4.9%, OR: 1.41). Furthermore, the mortality rate was much higher among patients testing positive for COVID, with 29% of patients positive for COVID succumbing to death versus 5.5% of patients COVID-negative (OR: 7.0).

Importantly, the poor outcomes observed in patients with STEMI treated during the pandemic persisted after correction for all potential confounding factors (geographic area, direct access by ambulance, ischemia time, door-to-balloon time, radial access, and type of stent). This discrepancy in outcomes after PCI remained even after exclusion of patients who tested positive for COVID-19. These findings illustrated that it may not be prudent to compare STEMI outcomes during the 2020 pandemic with STEMI outcomes from historic controls, as was conducted by the NACMI registry analysis.

The ISACS STEMI registry team also identified that during the pandemic, as expected, there was a significant reduction in PCI as compared with pre pandemic PCI. Interestingly, this reduction was not related to the incidence of COVID within a particular institution or to the number of patients positive for COVID, at both local and national levels in these European centers. Unfortunately, the incidence of PCI within specific Canadian and US sites in the NACMI registry was not reported, but this would be an interesting data point as this, too, could affect STEMI outcomes.

Although there is no perfect registry, database, or study, researchers are beginning to identify important signals from these analyses. Of equal importance, understanding distinct mechanisms related to the notable incidence of myocardial infarction in patients with COVID, especially concerning the ACE2 receptor and RAAS dysregulation, is rapidly advancing. Bridging this molecular work alongside registry and database findings is important in order to understand the clinical presentations and the optimal treatment options for patients with COVID and cardiovascular dysfunction. The collaborations that quickly formed among countries and hospitals in order to collect a large volume of patient data during the pandemic is commendable. Researchers who partook in these efforts will aid in the ongoing treatment of patients with COVID.

Unfortunately, these impressive efforts in studying COVID-19 may need to be revised and reinvented in a future pandemic. Epidemiologists fear that zoonotic diseases, such as COVID-19, will continue to occur. If the past holds true, the severity of each outbreak, including cardiac manifestations, may be unfathomably worse than the one before. Just as in the past, the tools that scientists and physicians will need most will be data collection and analysis in order to save lives.

Conflict of Interest

None of the authors has relevant financial disclosures related to this work.

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