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Coronavirus Disease and Acute Vascular Events

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The coronavirus disease 2019, also known as COVID-19 or SARS CoV-2, pandemic has created an unprecedented havoc worldwide. As of this writing, over 2.6 million individuals worldwide have been infected with this virus. This particular coronavirus does not appear to discriminate geographically and has spread to more than 177 countries. However, the infection rate and the resulting deaths are not the same in all the countries. Majority of affected countries have introduced some form of social distancing including mandatory lockdowns and bans of public gatherings. This mandatory isolation of the entire populations has created a catastrophic economic crisis. The Spanish Flu of 1918 infected a quarter of global population and killed an estimated 50 million individuals worldwide. However, cardiovascular disease (CVD) killed over 18 million individuals in 2016. Despite such a knowledge of the disease pandemics, at no time in the recent history, has there been such a worldwide lockdown of the global community. Researchers at the Harvard T.H. Chan School of Public Health have projected the transmission dynamics of SARS-CoV-2 through the postpandemic period in their latest article in *Science*. They speculate that the transmission of SARS-CoV-2 could resemble that of pandemic influenza and circulate seasonally after causing an initial global wave of infection.[1]

According to the Chinese researchers, clinical manifestation of COVID-19 is heterogenous.[2] Analysis of 1590 COVID-19 infected hospitalized patients in Wuhan, China, revealed that the mean age was 49 years. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). They found that circulatory and endocrine comorbidities were common among COVID-19 patients, leading to the conclusion that circulatory diseases remained the most common category of comorbidities.[2] In view of these observations and my own interest, I will limit my comments and discussions to the areas related to clinical and applied thrombosis/hemostasis.

Studies of COVID-19 patients in Wuhan, China, demonstrated that D-dimer levels upon admission >2.0 μg/mL effectively predicted in-hospital mortality. In view of this early observation, they concluded that D-dimer could be an early and helpful prognostic biomarker to improve the management of COVID-19 patients with CVD as a comorbidity.[3] On the other hand, in a study performed in COVID-19 patients in New York, with observed ST-segment elevated myocardial infraction, 64% had normal D-dimer levels according to Dr Bangalore and associates from the New York University Grossman School of Medicine.[4] The ways in which the novel coronavirus provokes cardiac injury are neither new nor surprising, according to the Harvard researchers, Prof. Peter Libby and Prof. Ridker (Coronavirus and the Heart, The Harvard Gazette, April 16, 2020). Myocardial injury in patients with COVID-19 could be due to plaque rupture, cytokine storm, hypoxic injury, coronary spasm, microthrombi, or direct endothelial or vascular injury.

Of the total hospitalized COVID-19 patient population, 89% had at least 1 preexisting chronic conditions according to the Centers for Disease Control. Approximately 50% reported hypertension and obesity, a third reported diabetes, and a third had CVD. At the time of admission, COVID-19 patients reported as having at least 1 acute comorbidity: diabetes (10%-20%), hypertension (10%-15%), or other CVD and cerebrovascular diseases (7%-40%). Analysis of 1590 hospitalized patients in China revealed that the mean age was 49 years. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). They also found that circulatory and endocrine comorbidities were common among COVID-19 patients.[3] In a recent article published in *JAMA* (April 22, 2020), of the 5700 COVID-19 patients included from the New York City area, the most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%). Swiss researchers, on the other hand, reported that patients with hypertension (23.7%), diabetes (22%), and cerebrovascular disease (22%) were the most distinctive comorbidities.

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SARS-CoV-2 invades human cells by latching its spikes onto the ACE_2 receptor found on the surface of cells in the respiratory airways, lungs, heart, kidneys, and blood vessels. In view of these observations, concern exists as to whether patients with hypertension and diabetes are at increased risk of COVID-19 infection.[5] The answer is far from clear at the time of this writing. Current clinical evidence does not support stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19.[6] Renin–angiotensin–aldosterone system inhibitors should be continued in patients with COVID-19, which seems to be the position now supported by multiple specialty societies.[7]

Lung injury and acute respiratory distress syndrome (ARDS) have taken center stage as the most dreaded clinical complications of COVID-19. A report from the early days of the pandemic in Wuhan, China, described that 12% of patients had both elevated levels of cardiac troponin and abnormalities of electrocardiograms and ultrasound measurements. Chinese researchers studied 187 patients with COVID-19, of which 28% had myocardial injury, which resulted in cardiac dysfunction and arrhythmias. According to their observation, myocardial injury had a significant association with fatal outcome of COVID-19, while the prognosis of patients with CVD without myocardial injury were relatively favorable.[8] Authors speculated that inflammation may be a potential mechanism for myocardial injury. This report provides a detailed cardiovascular information of the association between underlying CVD, myocardial injury, and fatal outcomes of patients with COVID-19. As to the mechanism, they speculate that viral injury can damage myocardial cells through several mechanisms, including direct damage by the virus, systemic inflammatory response, destabilizing coronary plaque, and producing aggravated hypoxia. The authors suggest aggressive treatment for patients "at risk" of myocardial injury.

The most common pattern of coagulopathy observed in patients with COVID-19 is characterized by elevations in fibrinogen and D-dimer levels. This correlates with parallel rise in markers of inflammation (C-reactive protein). Unlike classical sepsis-mediated disseminated intravascular coagulation (DIC), the degree of activated partial thromboplastin (aPT) elevation is less than partial thromboplastin (PT) elevation. According to some reputed US researchers, a hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19 meeting International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC. This observed increased coagulopathy, seems to be not due to a bleeding diathesis, but rather a predominantly prothrombotic DIC, with high venous thromboembolism rates and pulmonary congestion, and microvascular thrombosis and occlusion, with high rates of central line thrombosis and vascular occlusive events (ischemic limbs, strokes). Neurologists around the world say that a small subset of patients with COVID-19 are developing serious impairments of the brain. Similar observations have been made in Italy of COVID-19 patients having stroke, seizures, encephalitis-like symptoms, and blood clots, as well as tingling or numbness in the extremities.[9] Dr Thomas Oxley, the CEO of Synchron and neurointerventionist at Mount Sinai Hospital, New York, reported 5 young COVID-19 patients with symptoms of stroke.[10]

Researchers at the Division of Bioinformatics and Computational Biology, Chapel Hill, North Carolina, have used a systems biology approach for uncovering novel pathways by which viruses interact with host signaling, and expression networks, to mediate disease severity.[11] Acute lung injury (ALI) and its more severe form, ARDS, are devastating end-stage lung diseases that can arise following a variety of acute insults to the lung epithelium and occur following infection with SARS-CoV, H5N1, and H1N1 influenza viruses in human subjects. Using transcriptomics, proteomics, modeling, and validation approaches, in targeted knockout mice, these investigators have developed a model of altered hemostatic balance, defined by expression of procoagulative and antifibrinolytic factors, resulting in induction of an exudative phase of diffuse alveolar damage after infection. The authors speculate that lethal SARS-CoV infection overwhelms the normally protective profibrinolytic signaling of the urokinase pathway, leading to overall dysregulation, including increased *Serpine1* expression, and severe lung disease. Since fibrin stimulates the production of profibrotic growth factors, the investigators monitored many profibrotic growth factors including Transforming Growth Factor (TGF-B), Connective Tissue Growth Factor (CTGF) and Platelet Derived Growth Factor (PDGF) and found elevated levels of these growth factors during SARS-CoV or influenza infection. They conclude that fibrin accumulation in the lung is a hallmark of ALI and ARDS, and a reduced capacity to cleave and remove fibrin deposits corresponds to a poor clinical outcome.

"We've only known about this virus for 4 months," says Donald Thea, a professor of global health at Boston University. "There's a real paucity of data out there." How very true these observations are? This novel virus is very new, complex, and quite lethal. We are discovering new clinical manifestations of this virus infection every passing day. In a comment in *NEJM* Journal Watch (March 25, 2020), the authors summarize the clinical manifestation of COVID-19 in following way: "The COVID-19 pandemic has transformed every aspect of life, including CVD medicine." The evidence base is primordial and is likely limited by several biases. The virus is both potentiated by and causes sometimes fatal CV disease. While elevated troponin levels are common and can indicate poor prognoses, the American College of Cardiology recommends testing only patients suspected of myocardial injury.[12] In a seminal article by Bikdeli et al, endorsed by multiple specialty societies, the authors summarize their findings in the following way: "Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. In addition, many patients receiving antithrombotic therapy for thrombotic disease may develop COVID-19, which can have implications for choice, dosing,

and laboratory monitoring of antithrombotic therapy. Moreover, during a time with much focus on COVID-19, it is critical to consider how to optimize the available technology to care for patients without COVID-19 who have thrombotic disease. Herein, we review the current understanding of the pathogenesis, epidemiology, management and outcomes of patients with COVID-19 who develop venous or arterial thrombosis, and of those with preexisting thrombotic disease who develop COVID-19, or those who need prevention or care for their thrombotic disease during the COVID-19 pandemic.[13]"

According to the latest American Society of Hematology, COVID-19 resources (COVID-19 and coagulopathy), in a study by Tang et al from Wuhan, China, 71% of nonsurvivors from COVID-19 met the ISTH criteria for DIC compared to 0.4% of survivors.[14] Elevated D-dimer at admission and markedly increasing D-dimer levels (3- to 4-fold) over time were associated with high mortality, likely reflecting coagulation activation from infection, cytokine storm, and impending organ failure. They recommend monitoring PT, aPT, D-dimer, and fibrinogen. Worsening of these parameters, specifically D-dimer, indicates progressive severity of COVID-19 infection and requires aggressive critical care. Researchers have begun enrolling some of the COVID-19 patients with ARDS-like symptoms to monitor "biomarkers" such as blood levels of clotting factors, D-dimers, fibrinogen, and other biomarkers, which will help identify patients who are most likely to benefit from thrombolytic therapies. Elevated plasmin(ogen) seems to be a common biomarker in people with hypertension, diabetes, CVD, and cerebrovascular diseases, who are susceptible to SARS-CoV-2 infection.[15] In view of these observations, treatment with low-molecular-weight heparin, tissue plasminogen activator, or antiproteases targeting plasmin seems to be a better option. In a recent study reported by Agnelli and associates in the *NEJM* (April 23, 2020), oral apixaban was found noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism.[16] If effective and safe, these therapies could save lives by reducing the recovery time and freeing up more ventilators for other patients in need. The American Hospital Association predicts that 96 million people in the United States will eventually get COVID-19. Should this occur, it would mean that a total of 960 000 people would need mechanical ventilation.

Finally, there is considerable debate as to why there is such a stark difference in the infection and rate of death due to COVID-19 in various countries, as well as various regions of a country. There are so many facts related to the COVID-infection that cannot be described rationally. For instance, Italy's case fatality rate (CFR) is 10 times higher than Germany's (BBC News). The ranking for CFR is as follows: Italy (11.39), United Kingdom (8.17), China (4.05), United States (1.92), South Korea (1.66), and Germany (1.0). Even within the United States, large differences in CFRs have emerged. As of April 20, Michigan had reported CFR of 7.6%, compared to Oregon's 3.8%. Italy has the highest CFR for COVID-19. One factor that experts suggest for this observation is relatively older population. However, Germany and Japan also have large number of elderly people but have very low CFR. Yet another disturbing fact related to COVID-19 infection is the disparity in the severity of this disease in certain ethnic groups and minorities. A 6-fold increase in the rate of death for African Americans living in the United States due to a now ubiquitous virus should be deemed unconscionable, as reported in a recent tissue of *JAMA* (April 15, 2020). What is currently known about these differences in disease risk and fatality rates? In Chicago, more than 50% of COVID-19 cases and nearly 70% of COVID-19 deaths involve African American individuals, although they make up only 30% of the population. Moreover, these deaths are concentrated mostly in just 5 neighborhoods on the city's South Side. In Louisiana, 70.5% of deaths have occurred among African Americans, who represent 32.2% of the state's population. In Michigan, 33% of COVID-19 cases and 40% of deaths have occurred among African American individuals, who represent 14% of the population.[17] Poor living conditions, health care disparity, and high incidence of metabolic diseases (cardiometabolic comorbidities) seem to contribute to the excess CFR in this ethnic group, as well as in minority communities.

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