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Guest Editorial

Coronavirus (COVID-19), Comorbidities, and Acute Vascular Events

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Coronavirus disease pandemic has created a public health havoc worldwide. In. view of the mandatory lockdown in majority of countries, it also has caused a great economic crisis. The Spanish Flu of 1918, infected quarter of the global population (500 million) and killed 50 million individuals. No pandemic in the history of this planet, has caused as much panic, fear, anxiety, and frustration as the coronavirus disease. The Covid-19 is affecting 212 countries and territories around the world. Antarctica is the only continent not yet reached by the 2019-20 coronavirus pandemic. At the time of this writing there are more than 3.8 million cases worldwide, with 270,000 reported deaths. Ranking according to the number of infections is as follows: USA (1.2 million), Spain (216,582), Italy (207,428, UK (182, 260), Germany (164, 316), France (130, 185), Russia (124, 054), Turkey (122, 392), Iran (96, 448), Brazil (92, 630) and China (82, 875). Despite this ranking for number of infections, the ranking for the of deaths is quite different; USA (73,667), United Kingdom (30,076), Spain (25,857), Italy (29, 684), France (24, 594), Germany (6,735), There are so many facts related to the COVID-19 infection, that cannot be described rationally. For instance, Italy's case fatality rate (CFR) is ten times higher than Germany's (BBC News). The ranking for CFR is as follows: Italy (11.39), UK (8.17), China (4.05), USA (1.92), South Korea (1.66), Germany (1.0). At the time of this writing, we will have to analyze the infection rate, number of deaths, disparities related to the geography, ethnicity, and comorbidities separately for each country. No generalizations can be made with any degree of accuracy. Although experts' say that it's too early to determine, what role different healthcare systems play, in the severity of the COVID-19 pandemic, it's undeniable that each country's health care structural organizations, influence its public health response, when faced with such unprecedented virus disease pandemic.

Experts are trying to figure out, why the coronavirus wallop some places, and spare others? Despite its spread to all the countries on earth, global metropolises like New York City, Paris, and London have been devastated, while densely populated cities like Bangkok, Baghdad, New Delhi, Dhaka, Karachi, and Lagos have, so far, largely been spared. There is already an explosion of studies underway around the world, looking into how demographics, pre-existing conditions, and genetics might affect the wide variation impact (New York Times May 3, 2020). Since my interest is cardiometabolic diseases, I will be limiting my discussions, to the impact of comorbidities on the severity of COVID-19 infection. Scientists worldwide, are trying to figure out most effective policies, that worked in mitigation, tracing the infection, and containment. Hong Kong seems to have given the world, a lesson in how to effectively prevent COVID-19. With a population of 7.5 million, it has reported just 4 deaths, due to this virus infection. Researchers studying Hong Kong's approach, have already found that swift surveillance, mitigation (social distancing), tracing the infected individuals, and containment of the disease, to the 'hot spots' (quarantine) is very effective in limiting the outbreak of this highly infectious virus.

Influenza virus is most transmissible, just before the onset of symptoms, whereas SARS, is most transmissible, at 7 to 10 days after onset of symptoms. The COVID-19 is highly infectious, in the 2 days before symptom onset. In symptomatic patients, nasal swabs have yielded higher viral loads than throat swabs [1]. Studies from Wellcome Sanger Institute, UK, have explored viral entry associated genes and demonstrated the presence of transcripts in specific respiratory, corneal and intestinal epithelial cells. They conclude that these genes are co-expressed in nasal epithelial cells, highlighting the cells potential role in the initial infection, spread, and clearance [2]. Researchers in the US and UK have identified, hundreds of mutations to the virus. The big question is, which of these mutations do anything, to change the severity of infectiousness of the disease? One mutation-D614G, seems to be more dominant and could make the disease more infectious.

African Americans represent 13.4% of the American population, but counties with higher minority populations account for more than half of all Covid-19 cases and almost 60% of deaths. A 6-fold increase in the rate of death for African Americans living in the US, due to a now ubiquitous virus should be deemed unconscionable [3]. Poor living conditions, healthcare disparity and high incidence of metabolic diseases (cardiometabolic comorbidities), seems to contribute to the excess case fatality rate (CFR) in this ethnic group, as well as in

minority communities. In view of the fact, that New York City is the epicenter of the coivd-19 pandemic, in a recent article published in JAMA (April 22, 2020), a large COVID-19 case series from the New York City Area was reported. 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%) [4]. According to the Chinese researchers, clinical manifestation of COVID-19 are heterogenous. They reported their findings on 1590 Covid-19 patients and associated comorbidities and its impact on the severity of the disease, in a nationwide analysis [5]. Analysis of 1590 hospitalized patients in China, revealed that 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 patients with COVID-19 patients. Comorbidities, including hypertensions, obesity, diabetes, cardiovascular or circulatory diseases have consistently been reported to be common coexisting conditions among patients with severe COVID-19 illness.

Of the total hospitalized COVID-19 patient population in the USA, 89% had at least one pre-existing chronic condition according to the Centers for Disease Control (CDC), USA. Approximately 50% reported hypertension and obesity, a third reported diabetes, and a third had CVD. In the early studies conducted in China, the most distinctive comorbidities were cerebrovascular disease (22%) and diabetes (22%). In a second study, again hypertension was the leading comorbidity (23.7%) and diabetes (16.2%). In a third study reported from China, 30% had hypertension and 12% had diabetes. Early studies have called attention to the role of overrepresentation of hypertension as a comorbidity among patients with COVID-19. Since most patients with hypertension were often treated with angiotensin-converting enzyme (ACE) inhibitors, there was quite a bit of concern, as to whether patients with hypertension and diabetes are at increased risk for COVID-19 infection [6]. Data in humans are too limited to support or refute these concerns. Current clinical evidence does not support, stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, in patients with COVID-19. Renin–angiotensin–aldosterone (RAAS) system inhibitors, should be continued in patients with COVID-19, seems to be the position, now supported by multiple specialty societies [7].

Patients with long-term coronary artery disease, and those with risk factors for cardiovascular disease (CVDs), seem to have heightened risk of developing an acute coronary syndrome [8]. Researchers from two academic hospitals from Wuhan, China, which was the epicenter of the COVID-19 pandemic, have published their observations in JAMA Cardiology [9,10]. Of the 416 COVID-19 patients admitted to the hospital, 82 (19.7%) had evidence of myocardial injury manifested by elevation of high-sensitivity troponin-1 (Tn1) levels. They also found, that patients with myocardial injury had higher in-hospital mortality rate (51.2%) [10]. 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' for myocardial injury. The coronavirus has largely spared the children. However, according to the New York Times (May 6, 2020), a mysterious illness called, "pediatric multisystem inflammatory syndrome" has affected 64 children in the New York City. This is similar to the Kawasaki syndrome, and both with a surge of inflammation, can have serious effects on the heart. John Warner, the president of American Heart Association(AHA), states, -"As a trusted resource for data and research, with an entry point in more than 2,400 U.S. Hospitals, the AHA is uniquely positioned, to gather data quickly and accurately (COVID2019-Registry)". We hope that this professional society will not only collect the data but also disseminate the data to the public, from time to time.

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 researchers, a hallmark of severe COVID-19 is coagulopathy, with 71.4% of patients who die of COVID-19 meeting ISTH criteria for DIC [11-15]. This observed increased coagulopathy, seems to be not due to a bleeding diathesis,

but rather a predominantly pro-thrombotic DIC, with high venous thromboembolism rates and pulmonary congestion and microvascualr thrombosis and occlusion, with high rates of central line thrombosis and vascular occlusive events (ischemic limbs, strokes). Researchers at the Division of Bioinformatics and Computational Biology, Chapel Hill, North Carolina, have developed a model of altered haemostatic balance, defined by expression of procoagulative and antifibrinolytic factors [16]. They conclude that fibrin accumulation in the lung is a hallmark of acute lung injury (ALI) and ARDS, and a reduced capacity to cleave and remove fibrin deposits corresponds to a poor clinical outcome. According to the American Society of Haematology (ASH), COVID-19 Resources (COVID-19 and Coagulopathy), in a study by Tang., *et al.* from Wuhan, China, 71% of the non-survivors from COVID-19, met the ISTH criteria for Disseminated Intravascular Coagulation (DIC) compared to 0.4% of survivors [17]. Elevated D-dimer at admission and 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.

Lung injury and acute respiratory distress syndrome (ARDS), have taken a centre stage as the most dreaded clinical complications of COVD-19. Patients with severe coronavirus disease associated with ARDS, have increased pulmonary inflammation, thick mucus secretions in the airways, elevated levels of cytokines, extensive lung damage, and microthrombus. Neutrophilia seem to predict poor outcomes in patients with severe COVID-19 and neutrophil- to- lymphocyte ratio seems to be an independent risk factor for the severity of the disease [18]. 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, plasmin, 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 [19]. In view of these observations, treatment with low molecular weight heparins (LMWH), tissue plasminogen activator (tPA) or with antiproteases targeting plasmin, seems to be a better option. In a recent study, reported by Agnelli and associates in the NEJM (9April 23, 2020), oral apixaban was found noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism [20]. 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 US will eventually get COVID-19. Should this occur, it would mean that a total of 960,000 people would need mechanical ventilation.

Shortage of ventilators is not unique to the USA. There will be a worldwide shortage if the COVID-infection continues to spread unchecked and infects large populations. According to the Chinese investigators, progressive hypoxia is a characteristic manifestation in the clinical course of severe and critically ill patients with COVID-19 Pneumonia. Oxygen therapy plays an important role in the alleviation of respiratory distress. Hyperbaric Oxygen (HBO)Therapy (HBOT) is the most powerful oxygen therapy known and may be the best choice of oxygen therapy for severe critically ill adult patients with COVID-19 Pneumonia [21]. Chinese researchers in Wuhan, China, performed HBO treatment in severe COVID-19 patients and concluded that, - "HBOT can effectively correct systemic hypoxia, benefit to improve circulation, and immune function. Early HBO treatment may improve the total efficiency of systemic support treatments, reduce the use of mechanic ventilation and lower mortality rate of severe or critically ill patients with COVID-19". Prof. Paul Harch of Department of Medicine, Section of Emergency Hyperbaric Medicine, Louisiana State University, New Orleans, concluded, "With just 3-8 HBOTs the patients were bridged through the hypoxemic crisis phase of the infection and successfully discharged from the hospital. The author suggests that HBOT applied earlier in the disease process would prevent the deterioration that leads to the significant morbidity and mortality of COVID-19 infection [22].

While discussing the role of comorbidities, countries with very high prevalence and incidence of cardiometabolic diseases such as diabetes (China and India), excess weight, obesity, and CVD (USA), should pay a great attention to the COVID-19 pandemic and consider every treatment option that can reduce or prevent morbidity and mortality in coronavirus disease patients with underlying comorbidities. China and India with high prevalence of diabetes, should look for the early markers of inflammation, altered status of thrombotic or coagulation conditions, and aggressively treat the patients with antithrombotic, thrombolytic or HBO therapies. We in India, are initiat-

ing some hyperbaric oxygen therapy studies with COVID-19 patients, using the 'Made in India' Tekna Hyperbaric Oxygen Chambers (US FDA510(K) cleared and CE Marked: (www.hyperbaric-chamber.com). We will report our findings in our future publications on this topic of great public health importance.

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Volume 3 Issue 6 June 2020