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MINI-REVIEW ARTICLE

Cardiovascular Complications in Major 21st Century Viral Epidemics and Pandemics: an Insight into COVID-19

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Abstract: There have many major history-defining epidemics and pandemics in the 21st century. It is well known that acute infections can cause cardiovascular (CV) complications, especially in those with underlying cardiac disease. The variation in rates and types of CVD complications in major 21st century epidemics and pandemics varies greatly. The coronavirus disease 2019 (COVID-19) pandemic has caused the turmoil of the century and has COVID-19 has resulted in substantial human and economic loss. The novelty of COVID-19 and emerging CV effects is a new entity. In this review, we discuss the major epidemics and pandemics of the 21st century and associated CVD complications.

Keywords: COVID-19, severe acute respiratory syndrome coronavirus 2, pandemic, epidemic, cardiovascular complications, epidemiology.

1. INTRODUCTION

On March 11th 2020, the World Health Organization characterized coronavirus disease 2019 (COVID-19) as a pandemic [1]. As of October 25th 2020, there were over one million deaths from 42 million cases spanning 200 countries [2]. As we face the economic turmoil of the century, understanding the virus and its function is imperative to stymie off future pandemic and economic consequences.

The definition of a pandemic is the global spread of an epidemic. An epidemic is defined as an outbreak that has spread across a geographical area. Outbreaks occur when the number of cases of a disease far exceeds the expected number of cases.

There have many major history-defining epidemics and pandemics in the 21st century. It is well known that acute infections can cause cardiovascular (CV) complications, especially in those with underlying cardiac disease [3, 4]. The novelty of COVID-19 and emerging CV effects is a new entity. In this review, we discuss the major epidemics and pandemics of the 21st century and associated CVD complications.

2. EBOLA EPIDEMIC

The first Ebola epidemic happened in December 2013, caused by the Zaire species. The case fatality rate was recorded to be 55% [5]. Over 20,000 people were infected in West Africa. The disease spread across countries, and cases were reported in Spain, the United Kingdom, Italy and the United States (US). There were 4 recorded cases and 1 death in the US [6]. A second outbreak occurred in mid-2019 in which over 2500 people were affected by the disease in Central Africa and 1700 deaths occurred [7]. Fig. (**1**) illustrates a timeline of major epidemics and pandemics with the respective number of deaths caused by each disease.

The Ebola virus disease was first described in the 1970's and originated from the Ebola river valley in central Africa. The disease is caused by viruses within the genus ebolavirus. The 3 species of ebolavirus that cause significant disease in humans are Zaire ebolavirus, Sudan ebolavirus, and Bundibugyo ebolavirus [6]. The virus is transmitted through contact with mucosal surfaces, skin or by injury with contaminated needles. After an incubation period of 4 to 10 days, symptoms of fever, malaise, nausea, vomiting, and diarrhea begin. Some of the complications include impaired coagulation leading to gastrointestinal hemorrhage, bruising and impaired clotting. The putative mechanism identified entails increased vascular permeability leading to intravascular volume depletion [8]. This results in circulatory shock and multi-organ dysfunction; signs of severe disease and pathological changes, and in fatal cases involve necrosis of internal organs including the liver, testis, and ovaries [9].

CVD was reportedly rare in patients with Ebola. Patients developed tachycardia in the later stage of the disease, which could be due to underlying hemorrhage. In patients with fatal infection, hypotension caused circulatory shock and eventual death [10].

3. ZIKA EPIDEMIC

The first outbreak reported was in 2007 in Micronesia, followed by epidemics throughout Pacific Islands in 2013 - 2014 [11]. Another epidemic, which started in Brazil in 2015, spread to over 50 countries. Over 1 million cases were

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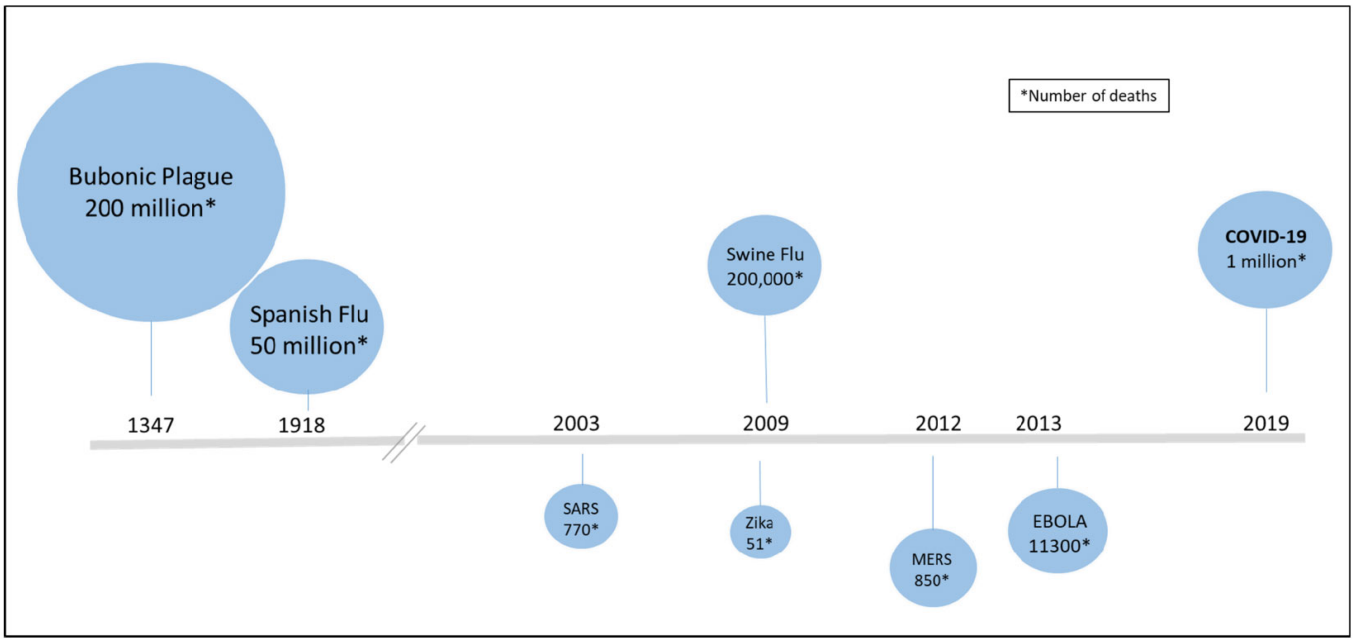

Fig. (1). The number of deaths caused by each disease is represented in the circle. ***Abbreviations:** SARS: severe acute respiratory syndrome; MERS: Middle East Respiratory Syndrome; COVID-19: coronavirus disease 2019. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

reported in Brazil, and over 1,000 cases were reported in the US [12].

The Zika virus was first discovered in 1947. The Zika virus infection is caused by virus transmission through the Aedes aegypti mosquito [13]. It is reported that the virus spreads through lymph nodes and blood circulation. It is important to note that those who become infected with the virus may be asymptomatic or develop mild symptoms such as fever, fatigue, arthralgia, conjunctivitis and a maculopapular rash [14]. The Center for Disease Control and Prevention reported the difficulty in detecting the spread of the virus due to the high proportion of individuals who are asymptomatic when infected as well the relatively long incubation period of two weeks [15]. The virus has been shown to cross the placental barrier and has been detected in the amniotic fluid of infected pregnant women. The disease in pregnant women can lead to miscarriage, microcephaly or stillbirth in the fetus [16]. Another major complication from Zika infection is the development of Guillan-Barre syndrome, a condition of autoimmunity against the peripheral nervous system, which can lead to paralysis [17].

There is evidence of the association between myocarditis with Zika infection; however, as the disease may be asymptomatic, CV complications may be under-diagnosed [18]. There are reports of the occurrence of arrhythmia in a series of 8 of 9 patients, of which 3 patients had atrial fibrillation, 2 patients had non-sustained atrial tachycardia and 2 patients had ventricular arrhythmias [19]. In the same study, heart failure was reported in 6 patients (of which 5 had reduced left ventricular ejection fraction).

4. SWINE FLU PANDEMIC

The first influenza pandemic of the 21st century was caused by H1N1, a new influenza virus, for which the disease was named Swine flu. Starting in 2009 and originating in Mexico, the virus spread across the world [20]. From April 2009 to July 2010, there were almost 500,000 lab-confirmed cases globally, but this number may be under-represented due to the mild symptoms of the disease [21]. In the US, 1 in 2000 people of those that presented with symptoms of Swine flu died, 1 in 400 required ICU admission and only 1 in 70 people affected required hospital admission [22]. The estimated global number of deaths within the first year due to a pulmonary cause to be 201,200 (range 105,700-395,600) and an estimated 83,300 cardiac deaths (46,000-179,900) [23].

Confirmed cases of Swine flu mainly had self-limited symptoms similar to influenzas such as fever, sore throat, cough, rhinorrhea and myalgia. It is reported that almost 40% of cases had gastro-intestinal symptoms such as vomiting and diarrhea [20]. Cases were characteristically affected children and young adults as compared to older age groups [24]. The incubation period for H1N1 is 2 to 7 days [25]. Although the disease is mild, complications include pneumonia, hemorrhagic bronchitis and death. Patients with underlying comorbidities such as CVD, chronic lung disease or are pregnant had higher rates of complications [26].

CV complications have been reported in Swine flu. Mild and transient effects reported are ST-T abnormalities on electrocardiogram, diastolic dysfunction and elevation of cardiac enzymes [27]. Case reports have described myocarditis

[28-30] and myocarditis leading to complete heart block [31]. Pericardial effusion and pericarditis leading to tamponade have also been reported [32]. In critically ill patients, right heart dilation and failure were prevalent [33].

5. CORONAVIRUSES

The coronavirus (CoV) species of viruses were first identified in the 1960's as the nomenclature was based on the appearance of the virus particle surrounded by a crown (corona) as visualized in microscopy [34]. Up until 2003, two strains (229E and OC43) of the virus were recognized. Currently, there are seven strains of CoV that are known to cause infection in humans, which generally self-resolve. It is estimated that CoV causes up to one-third of common colds but rarely causes lower respiratory tract disease. CoV are enveloped, single-stranded, positive-sense ribonucleic acid (RNA) viruses. The major diseases caused by CoV are Middle East Respiratory Syndrome CoV (MERS-CoV), severe acute respiratory syndrome CoV (SARS-CoV) and the newly identified SARS-CoV-2, which is better known as COVID-19 [35-37]. The diversity in phenotype and genotype of CoV can be attributed to the large genome base, RNA-dependent RNA polymerase and high frequency of RNA recombination [38].

5.1. Middle East Respiratory Syndrome (MERS)

In September 2012, MERS-CoV was first reported when a novel CoV strain was identified in Saudi Arabia [39]. The disease spread across 26 countries worldwide, from which there were over 1,600 laboratory-confirmed cases and almost 600 deaths [40].

MERS-CoV infects males more than females and displayed classic flu-like symptoms. The disease can cause severe complications, which include pneumonia, acute respiratory distress syndrome and even multi-organ failure [41-44]. Mortality rates have reported to be 20% to 60% of all cases and approximately 35%, according to the World Health Organization [40, 43, 45]. The prevalence of existing comorbidities was reported in 50% for diabetes mellitus and hypertension, while CVD was pre-existent in 30% of MERS patients [46]. Myocarditis has been reported to be a CV complication in MERS-infected patients resulting in fatality [47].

5.2. Severe Acute Respiratory Syndrome (SARS)

SARS-CoV was first reported in 2002 in Guangdong Province, China [48]. It spread across the globe to 29 countries and consisted of approximately 8000 cases with a mortality rate of 10% in infected individuals [48-50]. There were 8 confirmed cases in the US with 19 probable cases and no fatalities. The SARS-CoV outbreak cost a total of around $40 billion over 6 month period [34].

The typical symptoms of SARS-CoV were fever (38°C or higher), chills, cough, malaise and in some cases, pneumonia [51]. The presence of co-morbidities increased the mortality rate in patients with SARS. The prevalence of diabetes mellitus was reported to be 11% and CVD was 8%. The presence of either of these resulted in a 4-fold increase in mortality [52].

General CV complications were reported as hypotension and tachycardia that were found to be self-limiting; however, rarer complications were bradycardia, cardiomegaly and arrhythmia. Reversible cardiomegaly was reported in a sample of 13 patients (11%) without overt heart failure. Additionally, few cases reports described a cardiac arrest in patients with SARS-CoV [49, 53]. A 12-year follow-up study of 25 patients that recovered from SARS-CoV infection reported that 68% had hyperlipidemia, 44% had CV abnormalities and 60% had glucose metabolism disorders [54]. Given the long-term follow-up outcomes reported in this small-sized study and the close relation between SARS-CoV and SARS-CoV-2, the possibility of long-term CV complications should be monitored.

5.3. Covid-19 Pandemic

SARS-CoV-2 or COVID-19 first emerged in December 2019 in Wuhan, China. The strain of the virus was found to be the 7th known CoV and was similar to the strains of viruses that cause SARS and MERS [44, 49]. A major difference between these is that COVID-19 is widespread in the community, whereas nosocomial was more common form of transmission in SARS and MERS [55]. SARS-CoV-2 is thought to have originated from bats, similar to other strains of CoV, and shares up to 96% nucleotide identity with bat CoVs [56]. It is suggested that the virus went to the intermediate host of Malayan pangolin, which has a 91% nucleotide identity similarity, before infecting humans [57].

Emerging studies have reported the high prevalence of CVD in patients with COVID-19 [58]. CVD was reported to be more common in critically ill patients with COVID-19. More alarmingly, the cardiac injury was associated with a 4-fold increase in mortality despite adjusting for age and pre-existing CVD [59]. SARS-CoV-2 has impacted millions around the world in contrast to SARS-CoV and MERS-CoV. The importance of CVD in SARS-CoV-2 is an increasing concern and the higher rates of cases as compared to other CoV diseases has led to an accelerated need to understand CVD in COVID-19.

The exact mechanism of CVD in COVID-19 is unknown; however several mechanisms have been proposed and studied. It is thought that the virus causes infection in humans through binding of viral surface protein to human Angiotensin-Converting Enzyme 2 (ACE2) receptor after activation of the spike protein by transmembrane protease serine 2 [60]. The ACE2 transmembrane enzyme is primarily present on lung alveolar epithelial cells. The receptor consists of an 805-amino acid carboxypeptidase with a 17-amino acid N-terminal signal peptide and C-terminal membrane anchor [61, 62]. The enzyme catalyzes angiotensin I to angiotensin 1-9 and angiotensin II into angiotensin 1-7, which is key in vasodilation required to maintain hemostasis and blood pressure. The expression of ACE2 protein is predominant in lung alveolar epithelial cells, enterocytes, arterial smooth muscle cells as well as arterial and venous endothelial cells [63]. The ACE2 enzyme is known to be prognostic for heart failure, coronary artery disease and in patients with diabetes mellitus [64-66].

One theory of infectivity is based on direct myocardial involvement due to the presence of ACE2 receptors in the heart [67]. The utilization of the common entry pathway is thought to be the route for infectivity whereby the surface spike protein triggers the entry of the virus into the cell *via* the ACE2 receptor [62]. This entry is facilitated by a cellular protease, TMPRSS2, which cleaves the spike protein sites and allows fusion of viral and cell membranes [60]. The viral affinity to the ACE2 receptor has been shown to be a major determinant of infectivity rate [57]. A study reported low entropy of the viral associations with ACE2 receptor and low infectivity rate [57]. Another study reported that after internalization of the virus, the release of the virus into circulation leads to a cytokine storm which further leads to an inflammatory response that causes acute respiratory distress syndrome and CVD. Release of cytokines such as IL-6, IL-7, IL-22 and CXCL10 leads to myocardial injury, plaque instability and even plaque rupture thus causing downstream effects of acute coronary pathology. The hyperinflammatory state in COVID-19 leads to neutrophil activation, a higher neutrophil-to-lymphocyte ratio and activation of the coagulation system [68]. In addition, endothelial dysfunction in plaque stability in combination with activation of the coagulation cascade leads to end-organ damage and can affect microvasculature leading to myocardial ischemia [69]. Another model reports the precipitation of myocardial infection due to ACE2-dependence after pulmonary infection [70] and other reports suggest the combination of cytokine storm with an imbalance in T helper cell response lead to CV injury [71]. Indirect injury can also be caused by systemic inflammatory response or a combination of the factors above. Although not directly related to SARS-CoV-2, electrolyte imbalance in any critically ill patient can lead to cardiac rhythm disturbances. In particular, hypokalemia management in patients with COVID-19 is challenging to correct due to increased potassium loss due to ACE2 degradation [72]. In addition, the effects of antiviral drugs, corticosteroids and other treatments given to patients with COVID-19 may have adverse CV implications. The use of controversial antivirals in the treatment of COVID-19, namely hydroxychloroquine and chloroquine, can cause bradycardia, prolongation of PR interval and lead to atrioventricular block [73].

ACE2 carries single nucleotide polymorphisms, which can be restricted to certain geographical and ethnic groups [74]. There is a polymorphic genetic variation of the ACE2 gene, which accounts for the range of different polymorphisms [75]. There are reported to be over 16,000 different polymorphisms. The disparity in certain ethnic groups is especially interesting as death from COVID-19 has been reported to be prevalent in African Americans and Asians populations that have been known to carry distinct ACE2 polymorphisms [76, 77]. However, the current contention is that disparity and disproportionate differences in morbidity and mortality in these populations are more likely due to social determinants of health as opposed to such genetic polymorphism variations [78]. However, at the present time, the contributory role of genetic polymorphism remains to be determined.

Symptoms of SARS-CoV-2 vary in severity and can cause mild influenza-like symptoms (fever, cough, shortness of breath) to severe interstitial pneumonia leading to acute respiratory distress syndrome [79]. Transmission of the disease is through respiratory droplets by close contact. The mean incubation period is reported to be 5 days (95% confidence interval 4.1-7 days) [69]. The overall mortality rate is reported to be varied, but there is an estimation of 2.3% which is lower than that of SARS (10%) and MERS (34%) [80]. Over 80% of those infected have mild symptoms, 14% require admission to hospital for management of symptoms and 5% require admission to intensive care. Prognosis is grim for those admitted to intensive care with a reported 80% mortality rate [77].

It is known that patients with pre-existing comorbidities such as CVD are prone to developing a more severe illness of COVID-19 and have a higher risk of myocardial injury and increased mortality rate [58, 59]. The highest rate of fatality has been reported in those with pre-existing CVD and elevated levels of cardiac enzymes, in particular troponin T [58]. Fig. (**2**) demonstrates the mortality of patients with elevated and normal troponin T in patients with and without COVID-19. Elevated levels of brain natriuretic peptide were associated with a higher rate of intensive care unit admission in a case series [81].

A common CV complication described in COVID-19 with an incidence rate of 8-12% is acute myocardial injury, which is most commonly defined as troponin-I above the 99^{th} percentile upper reference range [82]. The presence of acute myocardial injury is associated with a worse prognosis in patients with COVID-19 [71, 79]. The development of arrhythmias is another common prevalent CVD. One study reported 17% of hospitalized patients with COVID-19 developed arrhythmias, which ranked second (after ARDS) for serious complications [79]. Moreover, the prevalence of arrhythmia was reported to be higher in patients admitted to ICU [44%] as compared to patients that did not require ICU admission (7%) [83]. Types of arrhythmias reported were conduction block, ventricular tachycardia, atrial fibrillation, ventricular fibrillation. There have also been cases of relative bradycardia despite fever and hypoxemia [84].

The development of myocarditis is a known complication of viral infection. There have been several reports of the development of myocarditis in patients with COVID-19 [85-87]. Myocarditis may, in turn, lead to arrhythmias and LV dysfunction. It is estimated that up to 7% of deaths in patients with COVID-19 are due to myocarditis [88]. The development of stress cardiomyopathy/Takostubo syndrome has been reported in patients with COVID-19 in multiple case reports [89-91]; however, the exact prevalence rate is unclear. A cohort study of 1,914 patients reports a significantly increased incidence of stress cardiomyopathy since the start of the COVID-19 pandemic [92]. The development of heart failure in patients with COVID-19 was reported to

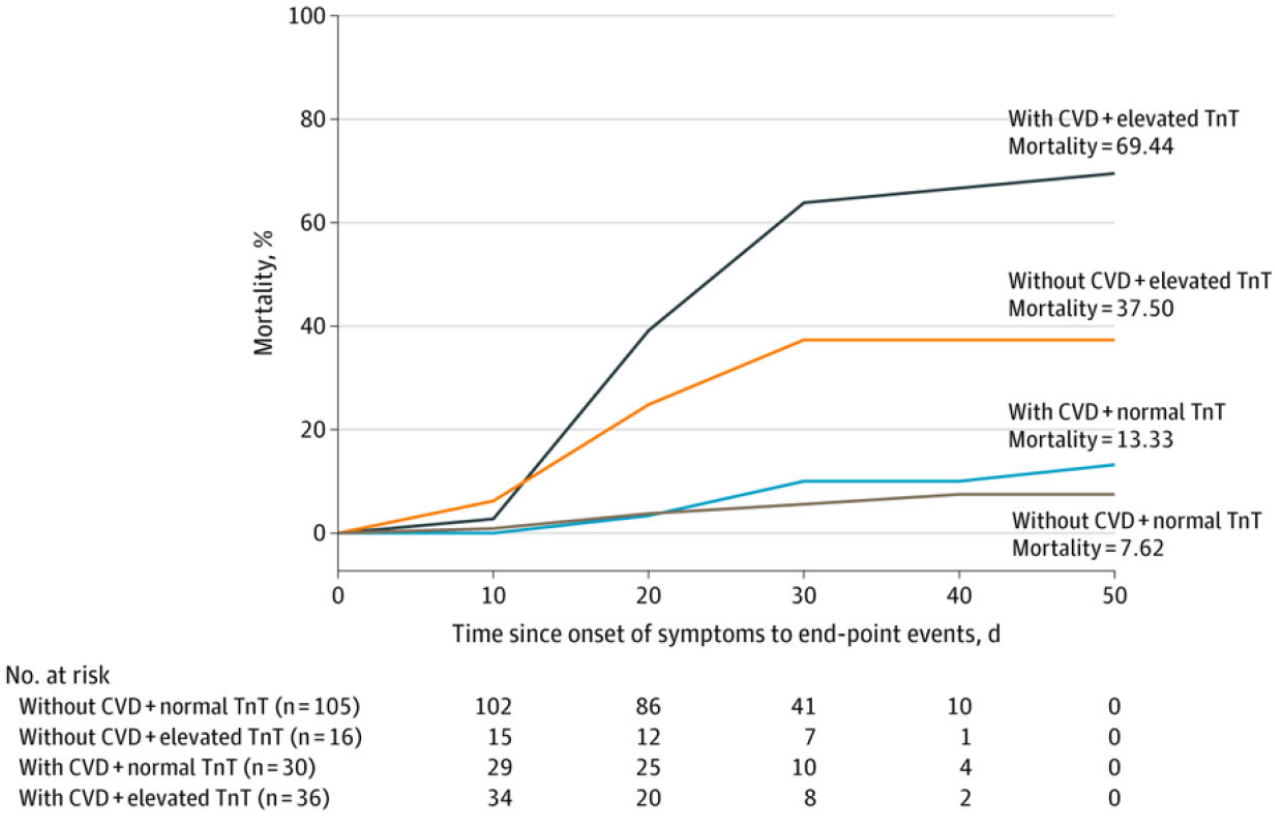

Fig. (2). Mortality of patients with coronavirus disease 2019 (COVID-19) with/without cardiovascular disease (CVD) and with/without elevated troponin T (TnT) levels cited from [58]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

be 23% in a study with 191 patients of a median age of 56 (interquartile range, 46-67 years) [71]. The rate of heart failure was 52% in those that died compared to 12% in those that survived. However, this was in select populations, so these percentages may not reflect real-world percentages given the rate of undiagnosed heart failure in these patients. The exact cause and mechanism of heart failure remain unclear. There is limited evidence on the prevalence of myocardial infarction in patients with COVID-19 however, type 2 myocardial infarction is known to be the most common type associated with viral infections. The development of coagulation abnormalities in patients with COVID-19 has been widely reported. Elevated D-dimer levels above 1g/L was found to be associated with worse in-hospital mortality [71]. The rate of disseminated intravascular coagulation was reported as 71% in non-survivors [93]. Other CV complications reported in patients with COVID-19 include pericarditis and vasculitis [58, 85]. In addition to the effect of COVID-19 on cardiac disease, the effect on cardiac surgical outcomes has been studied. 2 studies report all-cause mortality rate of 15% - 44% in patients that developed COVID-19 after cardiac surgery [94, 95].

With the novelty of this disease, there is a multitude of ongoing research investigations to understand the disease process and underlying pathologies [96]. The development of a prediction tool to calculate the estimated risk of COVID-19 positivity and individualize risk prediction was recently reported [97]. Other ongoing research work involves prediction tools with regard to COVID-19 diagnostics and outcomes. One study published a free online risk calculator based on a prediction model conceptualized using data from over 4,500 patients diagnosed with COVID-19. The calculator reports a predicted probability of hospitalization based on a range of factors such as age, race, ethnicity, gender, smoking status, body mass index, symptoms and comorbidities [98]. We can also surmise that it is while we see the acute effects of CV complications due to COVID-19, we expect the long-term effect on the CV system as we understand more of its infectious/inflammatory mechanisms.

CONCLUSION

The variation in rates and types of CVD complications in major 21st-century epidemics and pandemics varies greatly. COVID-19 and the association of CV complications is a new and evolving entity with a plethora of current research ongoing. COVID-19 has resulted in substantial human and economic loss. Understanding and keeping abreast with new developments in this field is paramount.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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