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Coronavirus Disease 2019 (COVID-19): Epidemiology, Clinical Spectrum and Implications for the Cardiovascular Clinician

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In December 2019, the first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan, China, during an outbreak of viral pneumonia. An initially regional epidemic has since rapidly expanded to a global pandemic affecting at least 124 countries with significant morbidity and mortality. At the time of this writing, the full magnitude of the public health impact has not been fully determined. More than 438,749 patients have been infected globally (55,243 U.S) and 19,675 have died.[1]

While containment and mitigation measures have intensified and disease-modifying pharmacologic compounds are being developed, COVID-19 continues to spread. In this Expert Opinion article, we provide a brief review of contemporary data pertaining to COVID-19 and discuss ways in which it interacts with the cardiovascular system.

Etiology

COVID-19 is caused by a novel, enveloped single-stranded RNA virus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is the seventh known coronavirus in humans and belongs to the same phylogenetic family as the 2002 SARS and the 2012 Middle East Respiratory Syndrome coronavirus (MERS-CoV-2). SARS-CoV-2 is presumed – but not confirmed – to have originated in bats given a remarkable (89-96%) genomic homology to bat coronaviruses.[2] SARS and MERS-CoV-2, the culprits of the two respiratory viral epidemics of the past two decades, similarly emerged from bats and infected civets (SARS) and camels (MERS-CoV-2) before spreading to humans.

Transmissibility and Case Fatality Rates

Despite sharing a vector, several differences exist between the three mentioned coronaviruses—most notably their transmissibility potential and case fatality rate. The basic reproductive number ("R0"), a measure of the expected number of cases that is generated from one case, is estimated to be 1.5-3.0 for SARS-CoV-2, as opposed to 0.5-1.0 and 1.5-4.0 with MERS-CoV-2 and SARS, respectively.[3,4]

SARS and MERS-CoV-2 were reported to have a 10% and 34.4% case fatality rate, respectively.[5] In contrast, SARS-CoV-2 has been estimated to have a case fatality rate of ~2.3%. The accuracy of

this assessment, however, is limited by disease ascertainment challenges, bias towards symptomatic and sick patients, and variability in testing accuracy.[6] With more comprehensive testing for COVID-19, particularly at earlier time points in the disease trajectory and among individuals with minimally symptomatic disease, a more accurate representation of its transmission dynamics and mortality trends will emerge.

Clinical Presentation

SARS-CoV-2 causes a respiratory infection with a highly variable clinical course that is dependent on host and organism factors. Mild disease, observed in 81% of patients in the initial Wuhan report, manifests as self-limited respiratory symptoms typical of a viral pneumonia, including fever, cough, dyspnea, sore throat but also, interestingly, anosmia and dysgeusia.[7] Severe disease, accounting for 14% of the cases in the same cohort, includes florid pneumonia which may progress to acute respiratory distress syndrome (ARDS) along with cardiogenic or distributive shock.

Subsequent studies, conducted in other geographic locations and patient populations, showed a different distribution of clinical severity among patients. Mortality rates associated with severe COVID-19 are high (8-25%), despite aggressive supportive measures including mechanical ventilation.[8,9] Individuals most vulnerable to developing severe and critical disease include those of advanced age or with significant comorbid conditions, such as cardiovascular disease, chronic obstructive pulmonary disease, and hypertension.

Impact of Cardiovascular Disease on Clinical Outcomes among Patients with COVID-19

The prevalence of cardiovascular disease among patients with COVID-19 is not fully established as most of the published reports focus on hospitalized patients who are more likely to have comorbid conditions than individuals with subclinical or mildly symptomatic disease. Pooling data from six studies (n=1527) revealed prevalence rates of hypertension, cardiovascular/ cerebrovascular disease and diabetes mellitus of 17.1%, 16.4% and 9.7%, respectively, among patients with COVID-19.[9]

Importantly, patients with severe disease and those admitted to intensive care units (ICU) had 2-3-fold higher rates of baseline cardio-metabolic conditions than non-severe/ICU patients.[9] For example, patients with history of coronary heart disease accounted for 5.8% of patients with severe disease but only for 1.8% of those with non-severe illness. Similarly, history of cerebrovascular disease was present in 2.3% of patients with severe disease and 1.2% in those with mild-moderate disease.[8]

In a review of 21 critically ill patients with COVID-19, rates of heart failure, diabetes mellitus and chronic kidney disease were 42.9%, 33.3% and 47.6%, respectively.[10] Patients with medical comorbidities had higher rates of in-hospital mortality, with diabetes mellitus (OR 2.85, CI 1.4-6.1, P=0.0062) and coronary heart disease (OR 21.4, CI 4.7-98.8, P<0.0001) showing an association with higher death rates in an univariable analysis.[11]

The reported association between hypertension and worse clinical outcomes could be mediated by vascular aging, diminished renal function, presence of non-adjusted comorbid conditions, or the effect of medications, and requires further study. Alternative mechanisms underlying the worse clinical outcomes in patients with cardiovascular disease may include more advanced age, reduced cardiopulmonary reserves, dysregulation of the immune system, and intolerance of viral-mediated cytokine storm.

COVID-19 and Cardiovascular Injury – Plausible Mechanisms

Although respiratory symptoms predominate, severe cardiovascular sequelae may occur with COVID-19. A plausible port for cellular binding of SARS-CoV-2 is angiotensin converting-enzyme 2 (ACE-2), a membrane-linked aminopeptidase and receptor through which the virus can potentially attach to respiratory structures and mediate tissue injury.[12] ACE-2 is highly expressed by type II alveolar epithelial cells in the lung and the invasion of these cells by SARS-CoV-2 is thought to provoke the respiratory symptoms. It has been suggested that using the same receptor, SARS-CoV-2 may attach and gain entry to cardiomyocytes and subsequently cause local inflammation although studies are needed to confirm that.

Since patients with hypertension and diabetes mellitus have higher expression levels of ACE-2, and given that the same patient populations tend to have more severe COVID-19 phenotypes, it has been hypothesized that higher ACE-2 levels could potentially augment viral entry and myocardial damage. Intriguingly, renin-aldosterone antagonists have been associated with increased ACE-2 expression and the use of such medications could increase the susceptibility to SARS-CoV-2 entry and proliferation.[13]

Despite being intriguing from a theoretical perspective, it is important to note that the precise biologic role of ACE-2 in patients with COVID-19, expression levels in diabetic or hypertensive individuals during times of acute viral illness, as well as the clinical value of pharmacologic renin-angiotensin-aldosterone blockage, merit further investigations and do not currently support dose modification of renin-angiotensin-aldosterone antagonists. The biochemical relationship between renin-angiotensin-aldosterone blockers and ACE-2 appears to be very complex, with some studies showing a protective effect, and there is currently no proof-of-concept in humans. As such, further rigorous studies are needed as is conveyed by a recent statement by the Heart Failure Society of American, the American College of Cardiology and the American Heart Association.[14] Interruption or dose-titration of such treatments could exacerbate cardiovascular and renal disease and should therefore not be pursued pending further data and recommendations.

Cardiac Injury

Emerging data suggests that SARS-CoV-2 infection may culminate in serious cardiovascular injury or worsening of existing cardiovascular disease. In the first reported COVID-19 cohort from China (n=41), five patients experienced acute cardiac injury with increased levels of high-sensitivity troponin (hs-cTnI >28 pg/ml) while only a single patient (4%) of those with mild disease showed

an elevation in troponin.[15] A larger subsequent report showed that 17% (24/145) of all patients had an elevated high-sensitivity troponin levels and that increased levels were strongly associated with survival status at discharge (elevated troponin: 46% among deceased, 1% among survivors).[11]

A meta-analysis of four studies, of which three used high-sensitivity immunoassays, demonstrated that severe COVID-19 (n=123), defined as requiring mechanical ventilation, ICU admission, or resulting in death, was associated with higher troponin levels compared to those with milder disease (standardized mean difference, 25.6 ng/L; 95% confidence interval, 6.8–44.5 ng/L).[16] In addition, an analysis of 416 hospitalized patients with COVID-19 showed an association between cardiac injury (evident in 19.7% of patients) and higher in-hospital mortality (51.2%, 4.5%, P<0.001), although no specific data was provided on the incidence of troponin elevation among patients with non-severe disease.[17]

Cardiac biomarker elevation in patients with COVID-19 may be a marker of disease severity and predict both the likelihood of ICU stay and all-cause mortality. Importantly, when detected in isolation, absent clinical or electrocardiographic features of acute coronary syndrome, an elevated troponin is most likely a reflection of the severity of the underlying illness and should not lead to further investigations or therapies, unless new clinical signs or symptoms emerge. However, if coupled with clinical indicators of myocardial infarction, guideline-directed interventions should be pursued, including coronary angioplasty, as long as supported by the available clinical infrastructure.

While several reports have implicated SARS-CoV-2 in cases of fulminant myocarditis,[18,19] the diagnostic methodology used in some was suboptimal. As such, these cases should be viewed as preliminary. Mechanistically, most of the myocardial injury seen with COVID-19 patients is likely related to effects of disease severity, cytokines, vasopressors, hypoxia, and disseminated intravascular coagulation (DIC).

When possible, it is important to perform cardiac magnetic resonance imaging or endomyocardial biopsy in suggestive COVID-19 cases, although it is recognized that such investigations may not be feasible in critically ill individuals. The natural history and clinical spectrum of SARS-CoV-2-mediated myocarditis, if corroborated as a clinical entity, remain unknown. For example, what treatments are likely to be effective? Would immunosuppressive therapies yield any benefit? Could intravenous gamma globulins play a role?

Patients with COVID-19 have also been shown to have abnormal coagulation parameters. This includes elevated levels of fibrin-degradation products and D-dimer, with the latter associated with an increased risk of in-hospital death (OR 18.4, 95% CI 2.6-128.6).[11] In a retrospective analysis of 183 patients in China with COVID-19, 21 (11.5%) died, of which 15 (71.4%) had evidence of DIC, a non-specific state of marked consumption of platelets and coagulation factors which is seen in a variety of fulminant medical conditions.[20] Non-survivors had significantly longer prothrombin and activated partial thromboplastin times compared to survivors. The incidence of

clinical venous thromboembolism among patients with COVID-19, however, is currently unknown.

Heart Failure/Arrhythmias

Another apparent cardiovascular sequela in patients with COVID-19 is heart failure. In a large cohort (n=191) from China, heart failure was reported in 44 (23%) patients and was significantly more frequent among non-survivors (52% vs 12%, p<0.0001).[11] A smaller US study (n=21) showed similar rates of cardiomyopathy (n=7, 33%).[10] Details regarding chronicity, type and class of heart failure have not been consistently reported. Whether cases of cardiomyopathy result from the underlying inflammatory state, hypoxia and hemodynamic impairment, or a direct effect of COVID-19, remains unknown. Furthermore, differentiating heart failure from ARDS and frequently associated hemodynamic insults is often challenging and further studies, particularly utilizing invasive hemodynamic measurements, are needed.

Cardiac arrhythmias have also been described in patients with COVID-19. In one report, 16.7% of hospitalized patients experienced an arrhythmia (of any type).[21] The development of an arrhythmia also correlated with greater odds of an ICU stay.

Pharmacologic Prevention and Treatment of COVID-19 – Cardiovascular Considerations

Numerous clinical trials are underway, assessing the efficacy and safety of various anti-viral treatments. Currently, there is no FDA-approved therapy to prevent or treat COVID-19. Remdesivir, a broad-spectrum anti-viral pro-drug that recently received an orphan drug label by the FDA, is currently under evaluation. Remdesivir has been shown to have potent anti-viral efficacy against Ebola virus, MERS-CoV, SARS-CoV and respiratory syncytial virus and is currently being evaluated for COVID-19 in NIH-sponsored randomized-controlled trials.[22] There are no known cardiovascular effects of Remdesivir, although ongoing studies will be helpful in further evaluating this.

Chloroquine, used to treat malaria and amebiasis, and its derivative, hydroxychloroquine, used in the management of systemic lupus erythematosus and rheumatoid arthritis, is also currently being tested in patients with COVID-19.[23] The anti-viral effects of chloroquine involve its inhibition of viral entry via endosomes as well as suppression of tumor necrosis factor α and interleukin 6. Chloroquine use has been associated with QT/QTc interval prolongation (with rare torsade de pointes), but otherwise has a low risk of cardiotoxicity. Rare occurrences of sudden cardiac death have been reported with hydroxychloroquine, although drug overdose was reported in a majority of the fatalities.

Lopinavir/ritonavir, an HIV-based protease inhibitor, is also undergoing assessment. A single large randomized controlled trial in patients with severe COVID-19 failed to demonstrate a difference in time to clinical improvement or mortality at 28 days.[24] No serious cardiovascular adverse events, however, were reported. Importantly, protease inhibitors may increase low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels in as many as 50% of patients after

2 years of medication use.[25] In addition, given that statins are metabolized by cytochrome P450 3A4 (CYP 3A4), their levels may increase significantly in the presence of protease inhibitors, potentially resulting in myopathy.[26] Because lovastatin and simvastatin are contraindicated in conjunction with protease inhibitors, other statins should be used cautiously.

Finally, the FDA recently approved the use of convalescent plasma from recovered individuals in patients with severe or immediately life-threatening COVID-19, including those with hypoxia, septic shock or multi-organ failure.

Knowledge Gaps and Future Directions

COVID-19 is a novel viral contagion with ongoing and wide-reaching public health implications. The pathobiology, clinical characteristics and prognosis of the infection are being actively elucidated. An early signal of excess heart failure, myocardial injury (and myocarditis), and arrhythmias has already been documented. Detailed description of patients' past medical histories and pre-admission medications, as well as the specific types and clinical manifestations of reported COVID-19-related cardiovascular impairments, is paramount. To unravel the cardiovascular phenotype and clinical outcomes of patients with COVID-19, pathological studies, particularly utilizing tissue biopsies or autopsy specimens, would be of unique value.

Preclinical studies implicating the ACE-2 receptor as a potential vehicle for SARS-CoV-2-mediated respiratory dysfunction (and cardiomyocyte injury) require careful validation in the clinical setting before any scientific conclusion can be made. Although higher ACE-2 levels, seen in hypertensive and diabetic patients, can be a marker (or even a driver) of COVID-19 disease severity, the current evidence is insufficient and more information needs to be generated, specifically about the independent association between renin-angiotensin-aldosterone medications and ACE-2 levels with clinical outcomes.

Cardiovascular testing, including circulating troponins and cardiovascular imaging, should be performed as per the clinical indication as most of the cardiovascular events in patients with COVID-19 appear to be secondary to the overwhelming critical illness. Supportive cardiovascular therapies remain the standard of care at this time. As treatment options for COVID-19 are tested, it will be important to scrutinize the potential adverse cardiovascular effects and drug-drug interactions of these therapies. Mechanistic molecular analyses, as well as retrospective and prospective studies with robust diagnostic methodology, are needed to provide a granular understanding of the cardiovascular sequelae of COVID-19.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020. [epub ahead of print]
2. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med* 2020. [epub ahead of print].

3. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med* 2020;27:taaa021.
4. Cowling BJ, Aiello A. Public health measures to slow community spread of COVID-19*. J Infect Dis* 2020. [epub ahead of print].
5. Azamfirei R. The 2019 novel coronavirus: a crown jewel of pandemics? *J Crit Care Med (Targu Mures)* 2020;6:3–4.
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020. [epub ahead of print].
7. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis* 2020. [epub ahead of print].
8. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020. [epub ahead of print].
9. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020. [epub ahead of print].
10. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020. [epub ahead of print].
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054-62.
12. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875-79.
13. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020. [epub ahead of print].
14. European Society of Cardiology. Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers. (*European Society of Cardiology website*). 2020. Available at: *https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang* . Accessed March 20, 2020.
15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
16. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020. [epub ahead of print].
17. Shi S, Qin M, Shen B, et al. Association of cardiac Injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020. [epub ahead of print].
18. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020. [epub ahead of print].
19. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020. [epub ahead of print].
20. Tang N, Li D, Wang X, Sun Z. Abnormal Coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:844-47.

21. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020. [epub ahead of print].
22. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.
23. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020. [epub ahead of print].
24. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020. [epub ahead of print].
25. Penzak SR, Chuck SK. Management of protease inhibitor-associated hyperlipidemia. *Am J Cardiovasc Drugs* 2002;2:91–106.
26. Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. *J Clin Transl Endocrinol* 2017;8:6–14.