

## MINI-REVIEW ARTICLE

## Cardiovascular Manifestations of COVID-19

Sneha Nandy<sup>1,\*</sup>, Siu-Hin Wan<sup>1</sup> and Jorge Brenes-Salazar<sup>1</sup><sup>1</sup>Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, USA

**Abstract:** Coronavirus disease 2019 (COVID-19) first emerged in a group of patients who presented with severe pneumonia in Wuhan, China, in December 2019. A novel virus, now called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), was isolated from lower respiratory tract samples. The current outbreak of infection has spread to over 100 countries and killed more than 340,000 people as of 25<sup>th</sup> May, 2020.

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The predominant clinical manifestation of COVID-19 is a respiratory disease- ranging from mild flu-like symptoms to fulminant pneumonia and Acute Respiratory Distress Syndrome (ARDS). Patients with pre-existing cardiovascular risk factors are considered more susceptible to the virus, and these conditions are often worsened by the infection. Furthermore, COVID-19 infection has led to de novo cardiac complications, like acute myocardial injury and arrhythmias.

In this review, we have focused on the cardiovascular manifestations of COVID-19 infection that have been reported in the literature so far. We have also outlined the effect of pre-existing cardiovascular disease as well as risk factors on the clinical course and outcomes of COVID-19 infection.

**Keywords:** COVID-19, cardiovascular, cardiac, coronavirus, SARS-CoV-2, infection.

## 1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) first emerged in a group of patients who presented with severe pneumonia in Wuhan, China. A novel virus, now called SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), was isolated from lower respiratory tract samples. The current outbreak of infections has spread to over 100 countries and killed more than 340,000 people as of 25<sup>th</sup> May, 2020.

Coronaviruses are enveloped positive-sense single-stranded RNA viruses, ranging in size from 80-220 nm in diameter. Whole genome sequencing of COVID-19 reveals that it is a novel beta-coronavirus distinct from SARS-CoV [1]. Guidelines from the National Health Commission of China suggest that droplets and close contact are the main routes of transmission, but the spread is also possible through aerosol-generating procedures in a closed environment for long periods [2]. The predominant clinical manifestation of COVID-19 is a respiratory disease- ranging from mild flu-like symptoms to fulminant pneumonia and Acute Respiratory Distress Syndrome (ARDS). Patients with pre-existing cardiovascular risk factors are considered more susceptible to the virus, and these conditions are often worsened by the infection [3]. Furthermore, COVID-19 infection has led to de novo cardiac complications like acute myocardial injury and arrhythmias.

In this review, we have focused on the cardiovascular manifestations of COVID-19 infection that have been reported in the literature so far. We have also outlined the effect of pre-existing cardiovascular disease as well as risk factors on the clinical course and outcomes of COVID-19 infection.

## 2. MATERIALS AND METHODS

A literature search was conducted using the PubMed/MEDLINE database. Original and review articles and recommendations from professional organizations published since December 2019 have been included. Keywords “COVID-19” and “coronavirus” were used in conjunction with “cardiac”, “cardiovascular”, “arrhythmia”, “myocardial injury”, “troponin” and “heart failure” and “coagulopathy”. A total of 413 results were found. Out of these, 56 were excluded, based on relevance. The final number of articles included was 357.

## 3. DISCUSSION

## 3.1. Pre-existing Cardiovascular Disease Risk Factors

Pre-existing cardiovascular disease has been shown to be a risk factor for disease severity and poor outcomes in COVID-19 infection [3]. In a study of patients with severe symptoms, 58% of the population was hypertensive, with cardiovascular diseases and arrhythmias being present in 25% and 44% of the subjects, respectively [4]. According to the National Health Commission of China, 35% of patients had a history of hypertension and 17% had a history of coronary heart disease [2]. Out of 1527 patients included in a me-

\* Address correspondence to this author at the Department of Cardiovascular Diseases, Mayo Clinic, 200 First St SW Rochester, MN 55905, USA; Tel: 7035815126; E-mail: [sneha.nandy@gmail.com](mailto:sneha.nandy@gmail.com)

ta-analysis of six studies, the incidences of hypertension and diabetes were twice as higher in patients requiring ICU admission as opposed to those who did not [3].

Increased BMI can also lead to increased vulnerability and mortality from COVID-19, as has been documented with viral diseases in the past [5]. In the setting of COVID-19, increased BMI has been associated with the severity of infection [6]. In an analysis by Peng *et al.*, a higher proportion of non-survivors (88.2%) had a BMI > 25 kg/m<sup>2</sup>, than the survivors (18.9%) ( $p < 0.001$ ) [7].

Longitudinal monitoring of the cardiometabolic health of patients with these risk factors will be helpful. In a 12 year follow-up of patients who recovered from SARS-CoV infection, it was found that dysregulation of lipid and glucose metabolism led to diabetes and cardiovascular disease [8]. Since SARS-CoV-2 is structurally similar to SARS-CoV, there is a need for cardiovascular protection for infected patients [9].

### 3.2. Acute Myocardial Injury

Acute myocardial injury in COVID-19 has been defined primarily as an elevation in serum myocardial markers above the 99<sup>th</sup> percentile upper reference range [10]. While hs-cTnI concentration is marginally elevated in all patients with COVID-19 infection, values exceeding the 99<sup>th</sup> percentile of the upper reference limit (URL) are observed in 8-12% of positive cases [11]. It is the most commonly reported cardiac abnormality found in patients with COVID-19 infection. Myocardial injury biomarker levels have been found to be significantly higher in patients requiring ICU admission than those who did not (median creatine kinase-MB level 18 U/l vs. 14 U/l;  $P < .001$ ; and high-sensitivity cardiac troponin I [hs-cTnI] level 11.0 pg/mL vs. 5.1 pg/mL;  $P = .004$ ) [4].

The exact conditions leading to acute myocardial injury are still unclear but have frequently been linked to acute myocarditis caused by COVID-19. Sporadic autopsy cases have suggested mononuclear infiltration of the myocardium [12]. Acute myopericarditis with severe left ventricular dysfunction (EF=35%) [13] as well as fulminant myocarditis with cardiogenic shock, with associated atrial and ventricular arrhythmias, have been described [14-16]. A rare case of life-threatening cardiac tamponade complicating myopericarditis associated with SARS CoV-2 infection has also been reported [17]. Myocardial injury and lung edema are hypothesized to arise from prompt and severe downregulation of myocardial and pulmonary ACE2 pathways [18]. Another contributory mechanism is hyper inflammation triggered by the inappropriate activation of cell-mediated immunity and the associated cytokine storm [9].

A study conducted by Chen *et al.* demonstrated that age, male gender, elevated NT-proBNP, cTnI, hs-CRP, serum creatinine, hypertension, and coronary heart disease were significantly correlated with critical disease status (all  $P < 0.05$ ) [19]. In a study of 334 patients from China, 82 patients (19.7%) had a myocardial injury. Greater proportions of pa-

tients with myocardial injury required a form of mechanical ventilation (either invasive or non-invasive) but those without myocardial injury did not. The mortality rate was higher in patients with myocardial injury than in those without it (42 of 82 [51.2%] vs. 15 of 334 [4.5%];  $P < .001$ ) [20].

### 3.3. Type 1 and Type 2 Myocardial Infarction

It has been documented in the literature that viral infections can lead to adverse cardiovascular events either by increased metabolic demand in the setting of the limited cardiac reserve (Type 2 MI) or by precipitating plaque rupture in the setting of inflammation and a prothrombotic state (Type 1) [21]. Severe respiratory infection, with both influenza and non-influenza viruses, has been identified as a risk factor for acute myocardial infarction [22]. As of April 2020, there have been no reported cases of acute coronary syndromes (ACS) (Type 1 MI) in the setting of COVID-19 [23].

A case of spontaneous coronary artery dissection (SCAD) has been reported in France [24].

The pattern of myocardial injury in COVID-19 patients is different from the usual rise and fall observed post-ischemia. Here, troponin levels have been observed to rise throughout the illness [25] and, in some cases, even go beyond what is typically observed in type II myocardial infarction [26]. Such patients also have higher levels of C-reactive protein (CRP), which appears to increase parallel to the troponin similar to what is seen with pro-brain natriuretic peptides. These observations suggest that a hyperinflammatory state contributes to non-ischemic myocardial injury [27].

### 3.4. Heart Failure

In a study of COVID-19 associated myocardial injury, 23% of patients were noted to have heart failure out of 191 inpatients. Heart failure was present in 52% of those who died and in 12% of those who recovered and were discharged. Heart failure was more common in non-survivors (52%,  $n = 28$ ) vs. survivors (12%,  $n = 16$ ) [28]. In a study of patients from Washington State, heart failure was observed in 33% ( $n = 7/21$ ) of ICU patients [29]. Reports of fulminant cardiomyopathy and cardiogenic shock are limited. Chronic heart failure has been associated with an increased risk of acute myocardial injury [20].

### 3.5. Thrombosis, Coagulopathy and Stroke

In a study of hematological parameters of COVID-19 patients, mild thrombocytopenia was observed in 20% ( $n = 13/65$ ) of the patients [30]. Zhou *et al.* defined Coagulopathy as a 3-second extension of PT or a 5-second extension of aPTT and reported this in 19% of subjects ( $n = 37$ ) [28]. In another study, Coagulopathy was present in 34.1% of patients ( $n = 42$ ) [25]. Antiphospholipid antibodies were detected in 3 patients with Coagulopathy and thromboembolic manifestations, as reported in a case report from China [31].

The incidence of thrombosis in COVID-19 patients has not yet been determined. About 50% of COVID-19 patients' disease progression is accompanied by an increase in D-

dimer levels. The level of D-dimer in severe patients is significantly higher than that in mild cases [32].

Elevated D-dimer levels ( $>1\text{g/L}$ ) have been associated with in-hospital death (adjusted OR 18.4,  $p=0.003$ ). In the same cohort, coagulopathy was present in 50% ( $n = 27$ ) of non-survivors vs. in 7% ( $n = 10$ ) of survivors ( $p < 0.001$ ) (28). In another report, disseminated intravascular coagulation was present in 71.4% ( $n = 15$ ) of non-survivors vs. 0.6% ( $n = 1$ ) of survivors [33].

Some investigators have evaluated the occurrence of venous and arterial thrombotic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, myocardial infarction, and systemic arterial events in COVID-19 patients.

In a study of 184 ICU patients on standard thromboprophylaxis, the combined incidence of thrombotic events was 31%. Venous thromboembolic events were the most common (27%) with the majority being PEs. Factors that were predictive of thrombotic events include increased age and evidence of Coagulopathy on screening tests- (prothrombin time [PT]  $> 3$  s above the upper limit of normal [ULN]), activated partial thromboplastin time [APTT]  $> 5$  s above the ULN) [34].

In another study of patients with Sepsis-induced coagulopathy score (SIC) $>4$ , administration of Low-molecular weight heparin (LMWH) for 7 days or longer was associated with a lower 28-day mortality rate [35].

In a cohort of 150 COVID-19 patients with ARDS, 25 (16.7%) developed Pulmonary embolism. Circuit clotting was observed in 28 out of 29 (96.6%) patients on renal replacement therapy, while thrombotic circuit occlusions oc-

curred in 2 out of 3 patients on extracorporeal membrane oxygenation (ECMO). It was also reported that patients with COVID-19-associated ARDS did not develop DIC and had markedly elevated levels of Von Willebrand factor (VWF) antigen, VWF activity, and factor VIII circulating in the blood [36].

Cases of stroke have also been reported as a complication of COVID-19 infection. Large-vessel stroke was reported as a complication in some cases of the 2004 SARS-CoV-1 outbreak in Singapore [37]. In a retrospective study from China, the incidence of stroke was 5%. The youngest patient was 55 years old [38]. A case series from New York described 5 cases of severe large vessel stroke (Mean NIHSS score=17) in patients younger than 50 years of age. The age group of patients ranged from 33 to 49 years. Only one patient had a prior history of stroke [39].

### 3.6. Arrhythmias

In a study of presenting symptoms for COVID-19 infection, palpitations were reported in 7.2% of patients. ( $n = 10$ ) [40]. In a study from China, the incidence of arrhythmias was 16.7% overall ( $n = 23/138$ ); Arrhythmia rate was also more frequent in ICU patients (44.4% vs. 6.9%;  $P < .001$ ). Further details of these manifestations were not provided but included atrial fibrillation, conduction disturbances, ventricular tachycardia, and ventricular fibrillation [4].

In another report, ventricular tachycardia/ventricular fibrillation was reported in 5.9% of patients ( $n = 11/187$ ). During hospitalization, patients with elevated TnT levels developed VT/VF arrhythmias more frequently (1.5% vs 17.3%,  $p < 0.001$ ) [25].

**Table 1. Summary of cardiovascular complications.**

Acute Myocardial Injury	-Defined as an Elevation of Myocardial Injury Markers $>99^{\text{th}}$ Percentile of URL -Incidence Ranges from 8% to 28%
Myocarditis	-Autopsy studies have yielded mononuclear infiltration -Most likely mechanism is severe downregulation of myocardial and pulmonary ACE -Has been reported in association with cardiogenic shock and cardiac tamponade
Type 1 MI	-No report of association yet
Type 2 MI	-Viral illnesses have been documented to cause increased metabolic demand in the setting of limited cardiac reserve. -Myocardial injury pattern in the case of COVID-19 appears to be due to hyperinflammation rather than ischemia.
Arrhythmias	- Palpitations and chest tightness have been reported as symptoms -More frequent in ICU patients -Includes atrial fibrillation, conduction disturbances, ventricular fibrillation, and ventricular tachycardia
Coagulopathy and Stroke	-Venous thromboembolic events documented in many patients, with pulmonary embolism being the most common - Mild thrombocytopenia and APLA antibodies have been reported in some patients -Increased D-dimer levels correlate with in-hospital mortality -Anticoagulation of hospitalized patients has been shown to reduce the 28-day mortality rate -Large vessel stroke has been reported, with some patients $<40$ years of age
Heart Failure	- Incidence has ranged from 23% to 33% -Associated with increased risk of myocardial injury -Associated with increased risk of mortality

Experts recommend a deeper understanding of arrhythmogenic risk in patients in all phases of illness, especially in recovery where hypoxia and electrolyte abnormalities often surface. This is essential to guide the need for arrhythmias monitoring (*e.g.*, mobile cardiac telemetry) post discharge, and to determine if an implantable (ICD) or wearable cardioverter defibrillator will be needed in those with impaired left ventricular function thought secondary to COVID-19 [41].

### 3.7. Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs)

It has been postulated that SARS CoV-2 enters host cells *via* ACE2 receptors, with a much higher affinity than SARS-CoV [42]. This has led to concerns about the use of ACE inhibitors and ARBs in affected patients because they can potentially upregulate the expression of ACE2 and increase susceptibility for viral entry [43].

Expert committees have now recommended that discontinuing these medications is not appropriate as they have significant cardiovascular and renal benefits. Despite the upregulation of the Renin-Angiotensin system, there is no evidence to support the theory of increased risk of viral entry or worse outcomes [44-46].

A recent article explored the possibility of using ARBs as tentative therapy prior to the development of acute respiratory distress syndrome [47]. There is a hypothesized down-regulation of ACE2 expression upon viral entry, which leads to unopposed local angiotensin II/ AT1R activity, which mediates acute inflammation of the lung. RAS inhibitors might exert a protective effect by decreasing angiotensin II/ AT1R activity and preventing the internalization of ACE-2 [48].

## CONCLUSION

There are myriad cardiovascular effects from infection with COVID-19, most notably including acute myocardial injury and arrhythmias. Predominant manifestations have been summarized in Table 1. These findings portend worse outcomes and, along with respiratory failure, may account for the cause of death among infected patients. Further research is needed to elucidate the epidemiology, pathophysiology, and management of cardiovascular diseases associated with COVID-19 infection.

## CONSENT FOR PUBLICATION

We, the authors, give consent for the publication and certify that this is original work that has not been submitted anywhere else.

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## CONFLICT OF INTEREST

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

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## REFERENCES

- [1] Zhu N, Zhang D, Wang W, *et al.* China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382(8): 727-33.  
<http://dx.doi.org/10.1056/NEJMoa2001017> PMID: 31978945
- [2] The National Health Commission of the People's Republic of China. Available from: <http://www.nhc.gov.cn/xcs/zhengcwj/202002/8334a8326dd94d329df351d7da8aefc2.shtml>
- [3] Li B, Yang J, Zhao F, *et al.* Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; 109(5): 531-8.  
<http://dx.doi.org/10.1007/s00392-020-01626-9> PMID: 32161990
- [4] 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; 323(11): 1061-9.  
<http://dx.doi.org/10.1001/jama.2020.1585> PMID: 32031570
- [5] Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, Whitmire JK. Obesity expands a distinct population of t cells in adipose tissue and increases vulnerability to infection. *Cell Rep* 2019; 27(2): 514-524.e5.  
<http://dx.doi.org/10.1016/j.celrep.2019.03.030> PMID: 30970254
- [6] Liu M, He P, Liu HG, *et al.* Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; 43(0): E016.  
<http://dx.doi.org/10.3760/cma.j.issn.1001-0939.2020.0016> PMID: 32062957
- [7] Peng YD, Meng K, Guan HQ, *et al.* Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi* 2020; 48(6): 450-5.  
<http://dx.doi.org/10.3760/cma.j.cn112148-20200220-00105> PMID: 32120458
- [8] Wu Q, Zhou L, Sun X, *et al.* Altered lipid metabolism in recovered sars patients twelve years after infection. *Sci Rep* 2017; 7(1): 9110.  
<http://dx.doi.org/10.1038/s41598-017-09536-z> PMID: 28831119
- [9] Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; 17(5): 259-60.  
<http://dx.doi.org/10.1038/s41598-020-0360-5> PMID: 32139904
- [10] Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China *Lancet* 2020; 395(10223): 497-506.
- [11] 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; 63(3): 390-1.  
<http://dx.doi.org/10.1016/j.pcad.2020.03.001> PMID: 32169400
- [12] Xu Z, Shi L, Wang Y, *et al.* Pathological findings of SARS-COV-2 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8(4): 420-2.
- [13] Inciardi RM, Lupi L, Zaccone G, *et al.* Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5(7): 819-24.  
<http://dx.doi.org/10.1001/jamacardio.2020.1096> PMID: 32219357
- [14] Zeng JH, Liu YX, Yuan J, *et al.* First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection* 2020; 48(5): 773-7.  
<http://dx.doi.org/10.1007/s15010-020-01424-5> PMID: 32277408
- [15] Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J* 2020; 42(2): 206.  
<http://dx.doi.org/10.1093/eurheartj/ehaa190> PMID: 32176300
- [16] Driggin E, Madhavan MV, Bikdeli B, *et al.* Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (SARS-COV-2) Pandemic. *J Am Coll Cardiol* 2020; 75(18): 2352-71.  
<http://dx.doi.org/10.1016/j.jacc.2020.03.031> PMID: 32201335
- [17] Hua A, O'Gallagher K, Sado D, Byrne J. Life-threatening cardiac

- tamponade complicating myo-pericarditis in SARS-COV-2 Eur Heart J 2020; 41(22): 2130.
- [18] Oudit GY, Kassiri Z, Jiang C, *et al.* SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009; 39(7): 618-25. <http://dx.doi.org/10.1111/j.1365-2362.2009.02153.x> PMID: 19453650
- [19] Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19. Zhonghua Xin Xue Guan Bing Za Zhi 2020; 48(7): 567-71. <http://dx.doi.org/10.3760/cma.j.cn112148-20200225-00123> PMID: 32141280
- [20] 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; 5(7): 802-10. <http://dx.doi.org/10.1001/jamacardio.2020.0950> PMID: 32211816
- [21] Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: Acute and long-term implications. Eur Heart J 2020; 41(19): 1798-800. <http://dx.doi.org/10.1093/eurheartj/ehaa231> PMID: 32186331
- [22] Kwong JC, Schwartz KL, Campitelli MA, *et al.* Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018; 378(4): 345-53. <http://dx.doi.org/10.1056/NEJMoa1702090> PMID: 29365305
- [23] Driggin E, Madhavan MV, Bikdeli B, *et al.* Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic J Am Coll Cardiol 2020; 75(18): 2352-71.
- [24] Courand PY, Harbaoui B. Spontaneous coronary artery dissection in a patient with COVID-19. J Am Coll Cardiol Intv 2020; 13(12): e107-8.
- [25] Guo T, Fan Y, Chen M, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019(COVID-19). JAMA Cardiol 2020; 5(7): 811-8. <http://dx.doi.org/10.1001/jamacardio.2020.1017> PMID: 32219356
- [26] DeFilippis AP, Chapman AR, Mills NL, *et al.* Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. Circulation 2019; 140(20): 1661-78. <http://dx.doi.org/10.1161/CIRCULATIONAHA.119.040631> PMID: 31416350
- [27] Cremer P. COVID-19 Curbside Consults Cleveland Clinic J Med 2020; 87(5) [www.ccjm.org](http://www.ccjm.org).
- [28] 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(10229): 1054-62. [http://dx.doi.org/10.1016/S0140-6736\(20\)30566-3](http://dx.doi.org/10.1016/S0140-6736(20)30566-3) PMID: 32171076
- [29] Arentz M, Yim E, Klaff L, *et al.* Characteristics and outcomes of 21 critically ill patients with covid-19 in washington state. JAMA 2020; 323(16): 1612-4. <http://dx.doi.org/10.1001/jama.2020.4326> PMID: 32191259
- [30] Fan BE, Chong VCL, Chan SSW, *et al.* Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020; 95(6): E131-4. <http://dx.doi.org/10.1002/ajh.25774> PMID: 32129508
- [31] Zhang Y, Xiao M, Zhang S, *et al.* Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020; 382(17): e38. <http://dx.doi.org/10.1056/NEJMc2007575> PMID: 32268022
- [32] Guan W, Ni Z, Hu Y, *et al.* Clinical characteristics of 2019 novel coronavirus infection in China. MedRxiv 2020. <http://dx.doi.org/10.1101/2020.02.06.20020974>
- [33] Tang N, Li D, Wang X, *et al.* Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18(4): 844-7.
- [34] Klok FA, Kruip MJHA, van der Meer NJM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-7. <http://dx.doi.org/10.1016/j.thromres.2020.04.013> PMID: 32291094
- [35] Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18(5): 1094-9. <http://dx.doi.org/10.1111/jth.14817> PMID: 32220112
- [36] Helms J. High risk of thrombosis in patients in severe SARS-CoV-2 infection: A multicenter prospective cohort study. J Intensive Care Med 2020. <http://dx.doi.org/10.1007/s00134-020-06062-x>
- [37] Umaphathi T, Kor AC, Venketasubramanian N, *et al.* Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004; 251(10): 1227-31. <http://dx.doi.org/10.1007/s00415-004-0519-8> PMID: 15503102
- [38] Li Y, Wang M, Zhou Y, *et al.* Acute cerebrovascular disease following COVID-19: A single center, retrospective, observational study. 2020; 5(3): 279-84. [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3550025](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3550025) preprint <http://dx.doi.org/10.2139/ssrn.3550025>
- [39] Oxley T, Mocco J, Majidi S, *et al.* Large vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020. 382: e60.
- [40] Liu K, Fang YY, Deng Y, *et al.* Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020; 133(9): 1025-31. <http://dx.doi.org/10.1097/CM9.0000000000000744> PMID: 32044814
- [41] Lakkireddy DR, Chung MK, Gopinathannair R, *et al.* Guidance for cardiac electrophysiology during the coronavirus (sars-cov-2) pandemic from the heart rhythm society sarscov-2 task force; electrophysiology section of the american college of cardiology and the electrocardiography and arrhythmias committee of the council on clinical cardiology american heart association. heart rhythm 2020; 17(9): e233-e241.
- [42] Li W, Moore MJ, Vasilieva N, *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003; 426(6965): 450-4. <http://dx.doi.org/10.1038/nature02145> PMID: 14647384
- [43] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8(4): e21. [http://dx.doi.org/10.1016/S2213-2600\(20\)30116-8](http://dx.doi.org/10.1016/S2213-2600(20)30116-8) PMID: 32171062
- [44] Thomas G. Renin angiotensin inhibitors in covid-19, covid-19 curbside consults cleveland clinic J Med 2020; 87(5)
- [45] European Society of Hypertension. Statement of the European Society of Hypertension (ESH) on hypertension, renin angiotensin system blockers and COVID-19. 2020, Available from: <https://www.eshonline.org/spotlights/esh-statement-oncovid-19-2/>
- [46] Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. American College of Cardiology <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19> [Accessed 2020].
- [47] Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 2020; 81(5): 537-40. <http://dx.doi.org/10.1002/ddr.21656> PMID: 32129518
- [48] Deshotels MR, Xia H, Sriramula S, Lazartigues E, Filipeanu CM. Angiotensin II mediates angiotensin converting enzyme type 2 internalization and degradation through an angiotensin II type I receptor-dependent mechanism. Hypertension 2014; 64(6): 1368-75. <http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.03743> PMID: 25225202