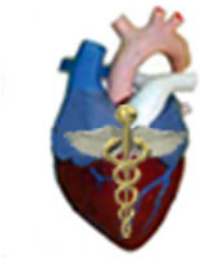
RHYTHMOS



April 2020 • Volume 15 • No 2 (58)

ISSN: 1792-7919 **e-ISSN: 1792-7927**

URL: www.rhythmos.gr / http://rhythmos.info.tm

EDITORIAL

Cardiovascular Complications of the Coronavirus (COVID-19) Infection

Antonis S. Manolis, MD,[1]* Theodora A. Manolis, MD[2]

[1] Athens University School of Medicine, Athens, Greece
[2] Red Cross Hospital, Athens, Greece
**E-mail:* asm@otenet.gr

Abstract

Apropos with the most recent emergence and disastrous and fulminant course of the new pandemic of the coronavirus (COVID-19) infection, relevant general and cardiovascular issues are herein discussed. ***Rhythmos*** 2020;15(2):23-28.

Key Words: coronavirus; COVID-19; cardiovascular disease; catheterization laboratory; ACE; ACE2; angiotensin receptor blockers

Abbreviations: ACE =angiotensin converting enzyme; AngII = angiotensin II; ARBs = angiotensin receptor blockers; ARDS = acute respiratory distress syndrome; CPR = cardiopulmonary resuscitation; cTnI = cardiac troponin I; CV = cardiovascular; CVD = cardiovascular disease; ICU = intensive care unit; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome; STEMI = ST elevation myocardial infarction

Introduction

After the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a new coronavirus epidemic emerged in late December 2019 in Wuhan, China, which quickly developed into a pandemic. This novel virus has now been named SARS-CoV-2 by the International Committee of Taxonomy of Viruses (ICTV). The virus can cause the disease named coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) refers to the virus as COVID-19 virus. On January 30, 2020, WHO announced that the COVID-19 outbreak was a Public Health Emergency of International Concern and declared it a pandemia (www.who.int/docs/default-source/ coronaviruse/20200307-cccc-guidance-table-covid-19-final.pdf?sfvrsn=1c8ee193_10). The numbers of affected patients increased exponentially by the end of March to over 900,000 cases with over 45000 deaths in 180 countries (www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6).

COVID-19 is a new disease that is distinct from SARS, Middle East respiratory syndrome (MERS) and influenza. Although coronavirus and influenza infections may present with similar symptoms, the virus responsible for COVID-19 is different with respect to community spread and severity. COVID-19 is spread through droplets and can live for substantial periods outside the body.

COVID-19 is a betacoronavirus, a typical RNA virus, like **SARS** and **MERS** viruses, presenting as ***viral pneumonia*** with a wide range of acute presentations. It

seems that this virus has greater infectivity rate when compared to SARS and MERS. The infectivity of COVID-19 is also much greater than that of influenza, as is its associated mortality (< 0.1% vs 0.5-4%);[1] COVID-19 mortality is much higher in elderly patients, and those with comorbidities.[2] COVID-19 mortality among patients who require hospitalization may be ~5-15%, and for those who become critically ill, it may range from 22% to 62%.[3-6] Progressive hypoxia and multiorgan dysfunction are the presumed causes of death.

According to a study on 138 hospitalized patients with confirmed COVID-19-related pneumonia in Wuhan, China, hospital-related transmission of COVID-19 was suspected in 41% of patients, 26% of patients were transferred to the intensive care unit (ICU), and mortality was 4.3%.[3] ICU patients (n = 36) were older (median age, 66 years vs 51 years), and more likely to have underlying comorbidities (72% vs 37%). In another report of 41 patients with COVID-19 pneumonia, complications included acute respiratory distress syndrome (ARDS) in 12 (29%), acute cardiac injury in 5 (12%) and secondary infection in 4 (10%); 13 (32%) patients were admitted to an ICU and 6 (15%) died.[7]

Symptomatology in COVID-19 infection is quite variable. Mild symptoms include common cold symptoms of viral infections (i.e. fever, cough, dyspnea, myalgias, fatigue, headache, and diarrhea) as well as laboratory abnormalities such as lymphopenia.[3, 7, 8] In severe cases, COVID-19 may present as viral pneumonia, ARDS, with or without non-cardiogenic or cardiogenic shock, to which elderly populations with preexisting comorbidities are the most vulnerable.[5] Loss of endothelial barrier function and resultant microvascular leak have been found to be a key determinant of the pathogenesis of bacterial sepsis (see discussion below).[9]

COVID-19 infection may have a direct impact on cardiovascular (CV) disease (CVD). Underlying CVD may predispose to COVID-19 infection. Those with CVD who are infected by the virus have an increased risk of CV complications.

CV Complications

Mostly case reports and series of patients afflicted by the coronavirus describe several cardiac problems, including high risk of mortality or complications in patients with underlying conditions. Almost 50% of patients who have been hospitalized have a chronic illness, with CVD observed in 40% of hospitalized patients. Approximately 20% of patients have developed ARDS, ~7% had acute cardiac involvement, 8.7% developed shock, 3.6% acute kidney injury and 16.7% cardiac arrhythmias.[3] Acute myocarditis has been consistently reported.[6]

Acute myocarditis. A recent meta-analysis of 6 studies from China comprising 1527 patients showed incident hypertension in ~17%, cardio-cerebro-vascular disease in ~16% and diabetes in ~10% of patients with COVID-19 with higher incidences reported in ICU/severe cases (2-fold for hypertension, 3-fold for cardio-cerebro-vascular disease and 2-fold for diabetes).[8] At least 8% of patients with COVID-19 suffered acute myocarditis, with an incidence ~13-fold higher in ICU/severe patients compared with the non-ICU/severe patients.

A recent meta-analysis of 4 studies reporting on cardiac troponin I (cTnI) in 341 patients with COVID-19 (36% with severe disease) indicated that the values of cTnI were found to be significantly increased in COVID-19 patients with severe disease than in those without (mean difference, 25.6 ng/L).[10] The authors hypothesized that initial measurement of cTnI immediately after hospitalization for COVID-19 infection, as well as longitudinal monitoring during hospital stay, may help identify a subset of patients with possible myocardial injury and thus predict the progression of COVID-19 towards a worse clinical picture. The use of echocardiography and/or cardiac magnetic resonance imaging to evaluate for myocarditis has not been adequately explored yet in these patients.

The mechanism of ***acute myocardial injury*** caused by COVID-19 infection might be related to angiotensin converting enzyme 2 (ACE2) (see discussion below), which is widely expressed not only in the lungs but also in the CV system. Other proposed mechanisms of myocardial injury include a cytokine storm and/or myocardial cell damage precipitated by respiratory dysfunction and hypoxemia.[7, 11]

Other CV events. The incidence of acute coronary events has not been reported yet in COVID-19 patients. Among 36 of 138 hospitalized COVID-19 patients, who were transferred to the ICU because of complications, ***arrhythmias*** were reported in 16 (44%), while the other reasons for ICU transfer included ARDS (22 or 61%), and shock (11 or 30.6%).[3] The incidence of ***heart failure*** has been reported at 23% among 191 patients, with a higher incidence noted among 54 non-survivors (52%) compared with 137 survivors (12%).[12] In patients with severe COVID-19 infection, particularly in non-survivors, abnormal coagulation results, especially markedly elevated D-dimer and fibrin degradation product, have been reported.[13] Furthermore, acute ***pulmonary embolism*** has also been reported.[14]

Mortality. According to a recent report of 72,314 cases from the Chinese Center for Disease Control and Prevention, the majority (81%) of cases were classified as mild (non-pneumonia and mild pneumonia), 14% were severe (dyspnea, respirations ≥30/min, oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24-48 hours), and 5% were critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[1] The overall case-fatality rate (CFR) was 2.3%, ranging from 0% in the group aged ≤9 years, to 8% in those aged 70-79 years and 14.8% in those aged ≥80 years. No deaths were reported among mild and severe cases. The CFR was 49% among critical cases. Case-fatality rate was elevated among those with preexisting comorbid conditions, 10.5% for CVD, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6% for hypertension, and 5.6% for cancer.[1] Among the 44,672 cases, a total of 1716 were health workers (3.8%). Overall, 14.8% of confirmed cases among health workers were classified as severe or critical and 5 deaths were observed.

According to a systematic review and meta-analysis of 19 articles and 39 case reports comprising 656 patients, 20% required ICU, 33% presented with ARDS, and 6% with shock.[15] A total of ~14% of hospitalized patients had fatal outcomes.

ACE2. The zinc metallopeptidase, angiotensin-converting enzyme (ACE), was discovered ~65 years ago,[16] and is a central component of the renin–angiotensin system (RAS). A dual role was assigned to ACE, including production of the potent vasoconstrictor octapeptide, angiotensin II (Ang II), from and by conversion of the decapeptide hormone, angiotensin I (Ang I), and the destruction of the vasodilator bradykinin.[17-19] ACE inhibition has been centerstage in the treatment of hypertension, congestive heart failure and myocardial infarction, endothelial dysfunction and renal disease, including diabetic nephropathy, for many years.[17] Almost half a century later (2000), a homologue of human ACE was discovered, ACE2.[18] ACE2 functions as a carboxypeptidase, expressed mainly in the heart, kidney and testis, with distinct differences in function from ACE; ACE2 removes single amino acids, unlike ACE which removes dipeptides, from the C-terminus of a peptide. Thus, ACE2 does not convert Ang I to Ang II and does not inactivate bradykinin. Interestingly, ACE2 is not inhibited by ACE inhibitors (ACEI).[19] Since its discovery in 2000, ACE2 has been implicated in heart function, hypertension and diabetes, with its effects being mediated, in part, through its ability to convert AngII to its metabolite, angiotensin-(1-7) (Ang 1-7). The physiological role of Ang 1-7 has not been fully elucidated but it appears to oppose the pressor, proliferative and pro-fibrotic actions of Ang II, acting through its own G-protein-coupled receptor, and functioning as an antihypertensive peptide. Thus, ACE and ACE2 seem to act as counterbalances in the RAS.[18, 20]

Beyond its involvement in CV pathophysiology, ACE and its effector peptide AngII have also been implicated in the pathogenesis of ARDS. As mentioned, recently, ACE2 was identified as the counter-regulatory enzyme of ACE that converts AngII into angiotensin-(1-7) and thus reducing the amount of AngII. By measuring ACE and ACE2 activity in bronchoalveolar lavage fluid, it has been shown that patients with ARDS have increased ACE activity and decreased ACE2 activity ($p < 0.001$) compared with the control group.[21]

Unexpectedly, ACE2 also was found to serve as a viral receptor and the cellular entry point for the SARS virus and the enzyme is therefore a prime target for pharmacological intervention on several disease fronts.[18] Investigators from China reported that COVID-19 uses the same cell entry receptor (ACE2) as SARS-related coronaviruses.[4, 22]

COVID-19 infection is triggered by binding of the spike protein of the virus to ACE2, which is highly expressed in the heart and lungs.[11, 18] COVID-19 mainly attacks alveolar epithelial cells, resulting in pneumonia. The symptoms are more severe in patients with CVD. Since ACE2 levels can be increased by the use of RAS inhibitors, the safety of ACEI or angiotensin- receptor blockers (ARBs) in patients with COVID-19 has recently been questioned.[11] However, other investigators have advanced the opposite suggestion that RAS inhibitors may have a protective role in COVID-19-associated lung injury, as based on animal experiments showing a downregulation of ACE2 by the virus infection in severe cases and an attenuation noted with administration of ACE2 or RAS blockers.[23-28]

On the other hand, in experimental animal models, another potentially protective drug group is the group of statins that have been shown to up-regulate ACE2 via epigenetic histone modifications.[29]

Underlying CVD. In patients with MERS and underlying CVD, a systematic analysis of 637 cases suggested that preexisting diabetes and hypertension (each prevalent in ~50% of patients), CVD (present in 30%) and obesity (16%) down-regulate the synthesis of proinflammatory cytokines and impair the host's innate and humoral immune systems.[30] Similarly, another study of 191 patients reported that 48% had a comorbidity, with hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%).[12] As mentioned, case-fatality rate was elevated among those

with preexisting comorbid conditions with highest rates of 10.5% reported for CVD.[1]

Mechanisms of increased CV risk. Mechanisms that lead to CVD seem to overlap with pathways that regulate immune function, such as age which is the strongest risk factor for CVD and also attenuates immune function and thus increases susceptibility to COVID-19.[2] Other traditional CVD risk factors such as diabetes and hyperlipidemia, influence immune function, while compromised immunologic status confers higher CV risk. An increased frequency of adverse CVD events occurring during COVID-19 infection might also affect prognosis, while COVID-19 infection itself may trigger pathways specifically related to COVID-19 that affect outcomes in CVD patients. A particularly vulnerable group of patients are the those who have received a heart transplant.[31] With regards to higher expression of ACE2 in CVD patients possibly enhancing susceptibility to COVID-19, see discussion above.

Chronic CVD. According to data accumulated from the experience of patients afflicted by and recovered from SARS- CoV infection, long-term CV system abnormalities were encountered in 44% of these patients, while hyperlipidemia was reported in 68%, and glucose metabolism disorders in 60%, possibly attributable to the use of high-dose pulses of corticosteroids in these patients during the acute phase of the disease. [32] However, virus-induced chronic damage to the CV system may also play a role. Given that COVID-19 has a similar structure to SARS-CoV, COVID-19 might also cause chronic damage to the CV system, and attention should be given to CV protection during treatment for COVID-19.[11]

Laboratory Testing

The WHO recommends that rapid collection and testing of appropriate specimens (respiratory material, such as naso- and oro-pharyngeal swab or wash in ambulatory patients and/or sputum, if produced, and/or endotracheal aspirate or bronchoalveolar lavage) from patients meeting the suspect case definition for COVID-19 is a priority for clinical management and outbreak control (https://apps.who.int/iris/handle/10665/331329). Suspect cases should be screened for the virus with nucleic acid amplification tests (NAAT), such as reverse transcription polymerase chain reaction (RT-PCR). In cases where NAAT assays are negative and there is a strong epidemiological link to COVID-19 infection, paired serum samples (in the acute and convalescent phase) could support diagnosis once validated serology tests are available.

Management

Although currently there are no effective therapies for COVID-19 and the development of a vaccine is several months away, a variety of pharmacologic agents are under active investigation.[33]

Antiviral agents have been used, like ribavirin and remdesivir which bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV2, and lopinavir/ritonavir that inhibits replication of RNA virus and has evidence of a synergistic effect *in vitro* with ribavirin.[34, 35]

In addition to antiviral agents, a plethora of immunomodulating and other medications to prevent complications that could arise from COVID-19 are currently being investigated. Chloroquine, which has been used as an antimalarial agent, blocks virus infection by increasing the endosomal pH required for virus/cell fusion, and has been demonstrated *in vitro* to have inhibitory activity in SARS-CoV2. [35]

Methylprednisolone is currently being used to treat severe cases of COVID-19 that are complicated by ARDS; however, evidence suggests that corticosteroids do not have an effect on mortality, but rather delay viral clearance. [36]

Support with extracorporeal membrane oxygenation (ECMO) is for the most critically ill patients.[37] ECMO provides direct support for the lungs and the heart by increasing systemic oxygen delivery and mitigating ventilator-induced lung injury, but it does not support other organs or prevent multiorgan failure.

Guidelines

General guidelines on the management of critically ill patients with COVID-19 have already been published, and include infection control, laboratory diagnosis and specimens, hemodynamic support, ventilatory support, and COVID-19 therapy.[38]

With regards to cardiac patients, experts have suggested that the use of guideline-directed therapies could offer additional protection to CVD patients during a widespread outbreak (statins, beta-blockers, ACEI, ARBs, aspirin); however, such therapies should be tailored to individual patients. Vaccinations are also important for patients with CVD, including pneumococcal and influenza vaccines. Patients who develop the coronavirus should be triaged based on the presence of underlying chronic diseases including CVD, respiratory and renal diseases so they receive prioritized treatment (www.acc.org/~/media/665AFA1E710B4B3293138D14BE8D1213.pdf).

According to a recent joint statement from the ***ACC Interventional Council and SCAI*** on issues facing **catheterization laboratory** personnel:[39]

● Elective cases should be postponed, especially patients with significant comorbidities or in whom the expected length of stay is >1-2 days / the number of people who scrub into procedures should be reduced

● Thrombolysis can be considered an option for the relatively stable STEMI patient with active COVID-19

● Appropriate personal protective equipment (PPE) should be worn including gown, gloves, goggles (or shields), and a N95 mask, during primary PCI in patients with active COVID-19 infection. The use of Powered Air Purifying Respirator (PAPR) systems may also be reasonable, especially for patients who may be vomiting (e.g. inferior STEMI), or those who may require CPR and/or intubation. Importantly, the vast number of catheterization labs have either normal or positive ventilation systems and are not designed for infection isolation. Therefore, catheterization labs will require a terminal clean following the procedure leading to delays for subsequent procedures.

● In selected cases with known COVID-19 and NSTEMI, (e.g., particularly for patients with type 2 MI) conservative therapy may be sufficient based on the patient's risk.

Important to note that recent reports suggest that acute cardiac injury is present in ~7% of patients with COVID-19 and may represent either type 2 MI or myocarditis.[3] Efforts should be made to try to differentiate between these Type 2 MIs vs. "primary" acute coronary syndromes

● All cath lab personnel should be fit-tested for N95 masks and be well versed in the proper techniques for doffing and donning PPE including eye protection.

● For patients with known COVID-19 or suspected COVID-19 who are required to come to the cath lab, the patient should wear a surgical mask, and all members of the cath lab team should put on PPE (preferably for aerosolized precautions given the risk of emergent intubation/suctioning/CPR).

Finally, with regards to concerns about the use of ACEI or ARBs in patients with COVID-19 infection, authorities have issued re-assuring statements, indicating that they recommend "continuation of ACEI or ARB medications for all patients already prescribed for indications such as heart failure, hypertension or ischemic heart disease", as "there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACEI or ARBs" (https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician).

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *Jama* 2020 Feb 24. doi: 10.1001/jama.2020.2648. [Epub ahead of print].
2. 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, March 17, DOI: https://doi.org/10.1016/j.jacc.2020.03.031.
3. 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 Feb 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print].
4. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol* 2020;92:418-23.
5. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. *JAMA Mar 11 doi: 101001/jama20203633 [Epub ahead of print]* 2020.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020 Feb 24[Online ahead of print].
7. 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.
8. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020 Mar 11. doi: 10.1007/s00392-020-01626-9. [Epub ahead of print].
9. Steinberg BE, Goldenberg NM, Lee WL. Do viral infections mimic bacterial sepsis? The role of microvascular permeability: A review of mechanisms and methods. *Antiviral Res* 2012;93:2-15.
10. 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 Mar 10. pii: S0033-0620(20)30055-4. doi: 10.1016/j.pcad.2020.03.001. [Epub ahead of print].
11. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020 Mar 5. doi: 10.1038/s41569-020-0360-5. [Epub ahead of print].
12. 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

Mar 11. pii: S0140-6736(20)30566-3. doi: 10.1016/S0140-6736(20)30566-3. [Epub ahead of print].
13. 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 Feb 19. doi: 10.1111/jth.14768.[Epub ahead of print].
14. Chen J, Wang X, Zhang S, et al. Findings of Acute Pulmonary Embolism in COVID-19 Patients *Lancet Infect Dis* 2020 http://dx.doi.org/10.2139/ssrn.3548771.
15. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis* 2020:101623.
16. Skeggs LT, Jr., Kahn JR, Shumway NP. The preparation and function of the hypertensin-converting enzyme. *J Exp Med* 1956;103:295-9.
17. Turner AJ, Hooper NM. The angiotensin-converting enzyme gene family: genomics and pharmacology. *Trends Pharmacol Sci* 2002;23:177-83.
18. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. *Trends Pharmacol Sci* 2004;25:291-4.
19. Acharya KR, Sturrock ED, Riordan JF, Ehlers MR. Ace revisited: a new target for structure-based drug design. *Nat Rev Drug Discov* 2003;2:891-902.
20. Ferrario CM, Chappell MC, Tallant EA, Brosnihan KB, Diz DI. Counterregulatory actions of angiotensin-(1-7). *Hypertension* 1997;30:535-41.
21. Wosten-van Asperen RM, Bos AP, Bem RA, et al. Imbalance between pulmonary angiotensin-converting enzyme and angiotensin-converting enzyme 2 activity in acute respiratory distress syndrome. *Pediatr Crit Care Med* 2013;14:e438-41.
22. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-73.
23. Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020 Mar 20. pii: ehaa235. doi: 10.1093/eurheartj/ehaa235.
24. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res* 2020 Mar 4. doi: 10.1002/ddr.21656. [Epub ahead of print].
25. Fedson DS, Opal SM, Rordam OM. Hiding in plain aight: an approach to treating patients with severe COVID-19 Infection. *mBio* 2020;11.
26. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436:112-6.
27. 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;11:875-9.
28. Shen L, Mo H, Cai L, et al. Losartan prevents sepsis-induced acute lung injury and decreases activation of nuclear factor kappaB and mitogen-activated protein kinases. *Shock* 2009;31:500-6.
29. Tikoo K, Patel G, Kumar S, et al. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. *Biochem Pharmacol* 2015;93:343-51.
30. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* 2016;49:129-33.
31. Michaels MG, La Hoz RM, Danziger-Isakov L, et al. Coronavirus disease 2019: Implications of emerging infections for transplantation. *Am J Transplant* 2020 Feb 24. doi: 10.1111/ajt.15832. [Epub ahead of print].
32. Wu Q, Zhou L, Sun X, et al. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. *Sci Rep* 2017;7:9110.
33. Li H, Zhou Y, Zhang M, et al. Updated approaches against SARS-CoV-2. *Antimicrob Agents Chemother* 2020 Mar 23. pii: AAC.00483-20. doi: 10.1128/AAC.00483-20. [Epub ahead of print].
34. Bhatnagar T, Murhekar MV, Soneja M, et al. Lopinavir/ritonavir combination therapy amongst symptomatic coronavirus disease 2019 patients in India: Protocol for restricted public health emergency use. *Indian J Med Res* 2020 Mar 11. doi: 10.4103/ijmr.IJMR_502_20. [Epub ahead of print].
35. Pang J, Wang MX, Ang IYH, et al. Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus: A systematic review. *J Clin Med* 2020;9.
36. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. *Intensive Care Med* 2020 Feb 26. doi: 10.1007/s00134-020-05967-x. [Epub ahead of print].
37. MacLaren G, Fisher D, Brodie D. Preparing for the most critically ill patients with COVID-19: The potential role of extracorporeal membrane oxygenation. *JAMA Feb 19 doi:101001/jama20202342[Epub ahead of print]* 2020.
38. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med* 2020 (in press).
39. Welt FGP, Shah PB, Aronow HD, et al. Catheterization laboratory considerations during the coronavirus pandemic: From ACC's Interventional Council and SCAI. *J Am Coll Cardiol* 2020 Mar 16. pii: S0735-1097(20)34566-6. doi: 10.1016/j.jacc. 2020.03.021.