Review Article

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COVID-19: Current Understanding of Pathophysiology

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ABSTRACT

Coronavirus disease 2019 has emerged as a global pandemic, affecting millions of people across the globe. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the human cell after binding to the Angiotensin-Converting Enzyme 2 receptors, that are present in various organs. The involvement of the respiratory system is common and may progress to acute respiratory distress syndrome. Besides the involvement of respiratory system other systems like cardiovascular, renal, gastrointestinal and central nervous are not uncommon. In-depth understanding of the pathophysiological basis of organs and systems involvement and disease progression aids in the safe and effective management of the COVID-19 patients. It also helps to guide future well-designed clinical trials, which is the need of time. This review aims to explore the current understanding of pathophysiological basis of various organ system involvement in patients with COVID-19, that can have relevance for patient management and future research. We reviewed the articles in various databases to assemble the current evidences.

Keywords: Coronavirus disease 2019; COVID-19; pathophysiology; severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The coronavirus disease 2019 (COVID-19) first emerged in China's Hubei Province in December 2019.[1] It has spread rapidly across the world as a pandemic, infecting individuals in several countries and causing significant morbidity and mortality. The virus that causes COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the beta coronavirus.[2] Efforts to fight against the disease is limited by an incomplete understanding of disease pathophysiology. Till date, the approach to hospital management of COVID -19 is based on limited data. A better understanding of disease transmission, pathophysiology and host immune response is essential for developing effective vaccines and therapeutics. It is the highest priority at this hour of crisis to develop validated and proven therapeutic measures to stop the explosive global spread of this pandemic.[3] In this review, we offer a comprehensive overview of the pathophysiology of COVID-19 on various organs and systems based on existing literature. Comprehensive review of the literatures was done to elicit the current understanding of pathophysiological basis of various organ system involvement in patients with COVID-19. Till date, only a few, if any therapies have proven to be helpful in patients with COVID-19. Only a few researches published are based on sound pathophysiological basis and concrete evidences that would guide management of patients with COVID-19 are lacking.[4] Proper understanding of pathophysiology can guide clinical management and form the basis for future clinical research in developing potential therapies.

METHODS

For this narrative review, the following databases were reviewed for published studies before August 20, 2020: PubMed, Google Scholar, and SCOPUS. We also searched pre-print servers including Research square, medRxiv, and SSRN. Boolean logic was used for conducting database search and Boolean search operators "AND" and "OR" were used to link search terms. Search terms "COVID-19", "SARS-CoV-2", and "novel coronavirus" were combined with terms "pathophysiology" and "pathogenesis" and the name of each organ system. The relevant articles were selected by the authors from the gallery of searched papers. This narrative review summarizes respiratory and non-respiratory manifestations of COVID-19 and their plausible pathophysiology.

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FINDING AND DISCUSSION

Respiratory system

SARS-CoV-2 gets access into human cells after binding to Angiotensin-Converting Enzyme (ACE2) receptor present in the airway epithelium and lung parenchyma. Direct injury to the lung tissue and the subsequent dysfunctional and excessive host response leads to the pulmonary symptoms. Rapid viral replication and vigorous cytokine response lead to lung epithelial and endothelial cell damage, eventually leading to hypoxia.[5] The degree of release of cytokines (tumor necrosis factor [TNF], IL-6, and IL-1ß) is directly related to the severity of symptoms.[6] Several therapies targeting cytokine response with anti-cytokine therapies or immunomodulators seem plausible in improving the outcome of COVID-19 patients. Alteration of endogenous surfactant system has been noticed in ARDS patients due to damage to type-2 epithelial cells and profound inflammation.[7] Clinical trials in ARDS have shown mixed results with exogenous surfactant use.[8-10] Surfactant protein has also been found to play an important role in treating viral pneumonia caused by Influenza A virus.[11]

Virus-induced downregulation of ACE2 may be one of the proposed mechanisms for disease pathology. Loss of ACE2 expression results in enhanced vascular permeability, increased lung edema, neutrophil accumulation and worsened lung function.[12] Blocking of the host target ACE2 receptor can be one of the potential therapeutic measures against SARS-COV-2.

Microvascular thrombosis has been demonstrated in lung tissue.[13,14] Pauci-inflammatory septal capillary injury with significant mural and luminal fibrin deposition and permeation of the interalveolar septa by neutrophils have been demonstrated in lung tissue of COVID-19 patients.[14] The underlying mechanism of pulmonary microvascular thrombosis may involve hypercoagulability, direct endothelial injury and complement activation. Clinical trials need to explore the therapeutic options for preventing and treating pulmonary microvascular thrombosis.

Acute Respiratory Distress Syndrome (ARDS) develops in 42% of patients presenting with COVID-19 pneumonia.[15] Gattinoni et al. described two patient subtypes: type-L and type-H according to the spectrum of ARDS.[16] In the type-L, patients present unique features with low lung elastance and low lung recruit ability but with severe hypoxemia.[17] Hypoxemia is likely due to loss of hypoxic vasoconstriction and impairment of pulmonary blood flow. Standard treatment for severe ARDS (prone positioning, and relatively high PEEP) may not show beneficial effects in recruitable lungs. Type-H patients have high lung elastance, higher lung weight, and respond to high PEEP.[16,17] However, this hypothesis is based on a few case series and anecdotal observations. Further clinical studies are warranted to better understand the COVID-19 ARDS and to explore the optimal ventilator management strategies.

Hypoxia is noticed in about 14% of patients.[18] Some of the hypoxic patients do not have respiratory distress, referred to as silent hypoxemia.[16] Patients experience respiratory distress only when there is severe hypoxemia or respiratory muscle fatigue.[19] In spontaneously breathing hypoxic patient when there is increased respiratory drive, the patient can develop lung injury termed as patient self-inflicted lung injury.[16,20]

Based upon the available data, similarities in terms of the clinical picture, pathophysiology and radiological findings have been postulated between COVID-19 and high altitude pulmonary edema. Medications like acetazolamide, nifedipine and phosphodiesterase inhibitors have been suggested as one of potential treatment choices to abate hypoxemia in COVID-19.[21,22] Apart from standard respiratory and ventilator support systems, alternative treatment strategies like hyperbaric oxygen therapy (HBOT) has been hypothesized to improve hypoxemia.[23] Preliminary evidence from the case report of patients with severe to moderate ARDS treated with HBOT showed significant improvement in hypoxemia and lung pathology without serious adverse events.[24,25] More research should be conducted to explore the potential role of HBOT.

Co-infection with other pathogens have been reported in patients with COVID-19 pneumonia.[26-28] Identification of another pathogen may not rule out the presence of the novel coronavirus.[26] Hospital-acquired pneumonia with resistant pathogens, was reported in 12% of intubated patients.[27] More data on co-infections are required to establish their importance in COVID-19 pathophysiology, severity and mortality.

Cardiovascular system

Recent evidence have suggested that cardiovascular involvement is common in COVID-19. Raised cardiac biomarkers in the form of hs-cTnI (high sensitivity cardiac Troponin I), LDH, CK-MB suggestive of myocardial injury has been demonstrated. one study demonstrated cardiac injury (elevated [hs-cTnI] or new ECG or echocardiographic abnormalities) in 7.2% of patients overall out of 138 hospitalized patients with COVID-19

in Wuhan China,.[29,30] Notably, hs-cTnI was above the 99th percentile of upper reference limit in 46% of non-survivors as opposed to one percent of survivors.[27]

There may be several mechanisms responsible for myocardial injury in patients with COVID-19. Direct invasion of cardiomyocytes and subsequent viral myocarditis is one of them. Structurally, the SARS-CoV-2 particle has a domain to bind to the ACE-2 receptors in the human epithelial cells.[31] Through this receptor, the virus binds to and invades human target cells. SARS-CoV-2 may also activate the ACE-2 receptor and upregulate ACE-2 downstream signal transduction via the Ras-ERK-AP-1 pathway.[32] This results in myocardial inflammation, fibrosis and exacerbation of cardiac dysfunction.

Cytokine storm has been postulated as another possible mechanism of myocardial injury in which there is overwhelming production of pro-inflammatory cytokines like interleukin-1ß (IL-1ß), IL-6, interferon-γ (IFN-γ), IFNγ inducible protein-10 (IP-10), monocyte chemo-attractant protein-1(MCP-1), granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-1α (MIP-1α) and tumor necrosis factor-α (TNF-α) among many in response to infection. significant elevation of these cytokines has also been seen in COVID-19 and are associated with disease progression.[33] one study by Liu et al demonstrated high amounts of inflammatory infiltrates in cardiac tissues pointing out to the inflammatory nature of tissue damage by SARS-CoV-2 infection.[34]

IL-6 is regarded as the most important among the cytokines and is also responsible for stimulating the production of other pro-inflammatory cytokines, the cumulative effect of which is vascular leakage and interstitial edema.[35] Additional effects of IL-6 may be papillary muscle contraction resulting in myocardial dysfunction.[36]

Unbalanced myocardial oxygen supply & demand and subsequent hypoxia is another mechanism of myocardial injury in COVID-19 patients.[37] The primary target of SARS Cov-2 is the lungs which can lead to hypoxia, hypotension and shock. Decreased oxygen supply to various organs including the heart and increased metabolic burden on cardiac tissues further aggravates the myocardial injury.[38] This effect may be more prominent in patients with underlying cardiovascular disease states.[39]

To conclude, overall management is mostly supportive with concomitant use of antiviral medications, steroids, intravenous immunoglobulins and ECMO (Extra Corporeal Membrane Oxygenation).[40]

Hematological system

COVID-19 infection is associated with significant thrombotic risks as proven by numerous studies. Infectious complications in critically ill patients can activate systemic coagulation pathways which can also lead to DIC.[41] Microorganisms and their components can induce the expression of numerous products, including tissue factor, by binding to pattern-recognizing receptors on immune cells.[42] Subsequent generation of tissue factor can induce host inflammatory reaction and generate pro-inflammatory cytokines. This can further activate coagulation cascade and lead to consumptive coagulopathy. All these responses act as an important link between humoral and cellular amplification pathways, a term also referred to as thrombo-inflammation or immune-thrombosis.[43,44]

Various components of microorganisms can also activate the intrinsic coagulation pathway.[45] Complement pathways can also contribute significantly in this process.[46,47] Pathogen-associated molecular mechanisms (PAMPs) are another essential aspect in this interaction between the immune response, coagulation pathway and sepsis.[42,48] Coagulopathy due to sepsis(SIC) can progress to DIC if the etiology of sepsis remains unaddressed.

SARS-CoV-2 infects the host using the ACE2 receptor. ACE2 receptors are also expressed by endothelial cells where viral replication occurs causing inflammatory cell infiltration, endothelial cell apoptosis, and microvascular prothrombotic effects.[49] Consistent with vascular endothelial dysfunction in sepsis-induced coagulopathy, an endothelialopathy appears to contribute to the pathophysiology of microcirculatory changes in SARS-CoV-2 infections.[50,51] Recent evidence shows the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death suggesting that SARS-CoV-2 infection facilitates the induction of endothelitis in several organs as a direct consequence of viral involvement and of the host inflammatory response.[49] Therefore, endothelial dysfunction acts as the principal determinant of microvascular dysfunction by shifting the vascular equilibrium towards more vasoconstriction with subsequent organ ischaemia, inflammation with associated tissue oedema, and a procoagulant state.[52]

In a meta-analysis by Xiong et al which included 1105 COVID-19 patients from nine studies, coagulation parameters were assessed for mild and

severe COVID-19.[53] Pooled results revealed that PT and D-dimer levels were significantly higher in patients with severe COVID-19. Increasing values of D-dimer and PT support the notion that DIC, may be common in COVID-19 patients.

In an analysis of 191 patients, factors associated with mortality included an elevated D-dimer, increased PT, elevations in IL-6, and other biomarkers of inflammation elevated troponin levels, and co-morbidities including older age, hypertension, diabetes, and coronary artery disease. All non-survivors met the definition of sepsis, and 50% had evidence of coagulopathy.[27]

Given this pro-thrombotic state hospitalized patients with confirmed or presumed COVID-19 infection should have coagulation testing performed on admission, including D-dimer, PT, aPTT, fibrinogen, and platelet count, testing that can provide useful prognostic information. All confirmed or suspected COVID-19 patients admitted to the hospital should be treated with pharmacologic VTE prophylaxis, given the high inflammatory state, unless there are specific contraindications especially given reports of microvascular thrombosis in early pathology specimens or pulmonary emboli.[54] Early autopsy reports demonstrated microvascular thrombosis as well as marked inflammatory changes.[55]

Renal system

Emerging evidence has supported the development of kidney injury due to SARS CoV-2 infection. A sequential investigation of 710 coronavirus positive subjects showed the presence of proteinuria in 44% and hematuria in 26.9% of patients. Raised plasma creatinine and blood urea nitrogen were observed in 15.5% and 14.1% of their patients respectively. Furthermore, the acute renal injury was found in 3.2% of infected individuals and was found to have a greater risk for in-hospital mortality.[56]

Various mechanisms have been postulated for the involvement of the kidney in COVID-19. Cytokine storm can cause AKI as a result of intra-renal inflammation, increased vascular permeability, volume depletion and cardiomyopathy, with subsequent cardiorenal syndrome.[27] The syndrome includes systemic endothelial injury, which manifests clinically as pleural effusions, oedema, intra-abdominal hypertension, third-space fluid loss, intravascular fluid depletion and hypotension. Cytokine storms can also lead to hypoperfusion-related injury of the renal tubules.[57,58] Injured renal tubular epithelium promotes the upregulation of IL-6, and human and animal studies increased IL-6 serum concentration in AKI were associated with higher alveolar-capillary permeability and pulmonary haemorrhage.[59] Rhabdomyolysis and raised creatinine kinase have been observed in few cases.[60] Dehydration can have various consequences on the kidney in the form of decreased GFR or AKI. In mild form, dehydration can be reversible but if severe it may result in acute tubular necrosis. Emerging evidence suggests the possibility of a direct cytopathic effect of SARS-CoV-2 since ACE2 receptor is highly expressed on podocytes and tubule epithelial cells.[61]

Gastrointestinal system

A recent meta-analysis of 4,243 COVID-19 patients found that the pooled prevalence of all gastrointestinal symptoms was 17.6%, which included anorexia,nausea/vomiting, diarrhea, and abdominal pain/discomfort.In the meta-analysis, the pooled prevalence of viral RNA positive in stool samples was 48.1%. Prolonged shedding of viral RNA in stool but not in respiratory samples was observed in 70.3% of patients, which lasted as long as 33 days after onset of disease.[62]

Manifestations like nausea, vomiting, and anorexia are non-specific subjective features and might have occurred due to generalized illness and antibiotics use. However, diarrhea is the objective manifestation of viral involvement in the gut. ACE2 is highly expressed in the esophagus and absorptive enterocytes from the ileum and colon.[63] Once infected by the virus, intestinal epithelial cells may become highly permeable to foreign pathogens, leading to poor absorption and diarrhea. Also, ACE2 is known to regulate intestinal inflammation and may also cause diarrhea.[64,65]

A retrospective study including 148 COVID-19 confirmed patients found that 55 patients (37.2%) had an abnormal liver function at hospital admission.[66] It is due to systemic inflammation, hypoxia associated with pneumonia, cytokine storms, and drugs induced hepatotoxicity. In the aforementioned, patients with liver injury had a higher level of inflammatory markers, namely CRP and procalcitonin. Besides, compared with patients with normal liver function, patients with abnormal liver function received a significantly higher proportion of hepatotoxic drugs lopinavir/ritonavir after admission.[66]

Neurological system

COVID-19 is found to be associated with myalgia, headache, encephalopathy and altered taste and smell sensation. However, COVID-19 can also present with severe neurological manifestations such as acute ischemic stroke (AIS), intracerebral hemorrhage,

encephalomyelitis, and acute myelitis, and Guillain-Barré syndrome (GBS).[67]

Neurons and glial cella express ACE2 receptors, making brain a potential target for COVID-19 infection.[68] However, the way the virus enters the brain is still nebulous. One plausible route of entry is through the olfactory nerve. Retrograde transfer into the axon whether through synapses, endocytosis, or exocytosis, could explain viral migration into the brain.[69-71] Another possible route for the entry of virus in the brain is through the blood. Since the capillary endothelium expresses ACE2 receptors, the slow movement of blood in the brain capillaries can promote viral interaction with endothelial ACE2 receptors. When in endothelium, the virus can infect and destroy the endothelium and bud off into the brain parenchyma, thereby promoting parenchymal infection.[68,72] Finally, it is well known that SARS-CoV-2 can cause a massive surge of cytokines, called a cytokine storm. The downstream effect of this immune response may be severe neuronal inflammation, leading to encephalitis and myelitis.[73,74]

GBS along with its variants have been reported to be associated with COVID-19. GBS is a post-infectious, acute inflammatory immune-mediated polyradiculoneuropathy presenting typically with paresthesia, neuralgia, ascending motor weakness and dysautonomia. The pathophysiology behind GBS is molecular mimicry and depending on its variants, the target of immune destruction are myelin sheath, Schwann-cell components and axolemma.[75] The majority of GBS patients have reported an antecedent respiratory or gastrointestinal illness in the 1 to 4 weeks before the presentation of GBS.[76] Mimicry between SARS-CoV-2 structural protein and nerve antigens are thought to be a major driving force behind the development of GBS in COVID-19[77]

It is known that the expression of the ACE2 receptor, and the ability of the ACE2 receptor to lower blood pressure, is reduced in patients with hypertension. In SARS-CoV-2 infection, the presence of S protein could further reduce the expression and function of ACE2 proteins. This could potentially lead to uncontrolled hypertension, arterial wall rupture, and cerebral hemorrhage in infected patients.[78] In addition, if the virus spreads in the capillaries of the brain, it may damage and tear the capillaries, leading to substantial bleeding.[68] Besides, COVID-19 patients have been reported to have thrombocytopenia and coagulopathy, both of which are contributory factors for secondary brain parenchymal hemorrhage.[79,80]

AIS is commonly reported in COVID-19 infected patients. Several assumptions support this manifestation of COVID-19. Through the ACE2 receptor of the vascular endothelium, the viral invasion of the endothelium may cause extensive endothelitis, increasing the risk of thrombosis leading to cerebrovascular events.[49]

In a group of severe COVID-19 patients with bilateral cerebral infarction, the levels of anti-phospholipid antibodies (including anti-cardiolipin and anti-β-2 glycoprotein) were elevated. This suggests that antiphospholipid antibodies may play a role in the pathophysiology of AIS in COVID-19 patients.[79]

AIS may also arise secondary to cytokine storm syndrome.[73] The massive release of cytokines can cause severe endothelial damage, disseminated intravascular coagulation, and disrupted cerebral auto-regulation, all of which increase the risk of ischemic stroke.[74] Besides, critically ill patients with severe SARS-CoV-2 infection often show elevated levels of D-dimer. It serves as a marker of dysfunctional activation of the coagulation system, with subsequent risk of AIS.[60,80,81]

CONCLUSIONS

In addition to the involvement of the respiratory system, patients with COVID-19 usually have multisystem involvement. A better understanding of the pathophysiology basis of organs involvement can aid in safer patient management and improved outcome. As the understanding of disease is ever evolving, with paucity of strong recommendations in the recent guidelines, pathophysiological basis of disease may help to formulate interim local policies, awaiting stronger evidences. It can also help to plan well-designed future clinical trials.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.[PubMed]
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565-74.[PubMed]
3. Rabaan AA, Al-Ahmed SH, Sah R, Tiwari R, Yatoo MI, Patel SK, et al. SARS-CoV-2/COVID-19 and advances in developing potential therapeutics and vaccines to counter this emerging pandemic. Ann Clin Microbiol Antimicrob. 2020;19(1):40. Published 2020 Sep 2.[PubMed]
4. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott

HC. Pathophysiology, transmission, diagnosis and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA. 2020;324:782-93.[PubMed]

5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80:607-13.[PubMed]

6. Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, et al. Clinical characteristics of 82 death cases with COVID-19. Preprint at medRxiv DOI https://doi.org/10.1101/2020.02.26.20028191

7. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis. 1993;147:218–33.[PubMed]

8. Wiedemann H, Baughman R, de Boisblanc B. A multi centered trial in human sepsis-induced ARDS of an aerosolized synthetic surfactant (Exosurf). Am Rev Respir Dis. 1992;145:A184.

9. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1997;155:1309–15.[PubMed]

10. Anzueto A, Baughman RP, Guntupalli KK, Weg JG, Weidemann HP, Raventos AA, et al. Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf acute respiratory distress syndrome sepsis study group. N Engl J Med. 1996;334:1417-21.[PubMed]

11. Hsieh IN, De Luna X, White MR, Hartshorn KL. The Role and Molecular Mechanism of Action of Surfactant Protein D in Innate Host Defense Against Influenza A Virus. Front Immunol. 2018;9:1368.PMC6008380

12. Imai Y, Kuba K, Penninger JM .The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Exp Physiol. 2008; 93:543–8.PMC7197898

13. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020;18:1559-61.[PubMed]

14. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res. 2020;220:1-13.PMC7158248

15. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:1-11.PMC7070509

16. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med. 2020;46:1099-102.[PubMed]

17. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "Typical" acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201:1299-300.[PubMed]

18. 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. ;323(13):1239-42.[PubMed]

19. Baldwin J, Cox J. Treating Dyspnea: Is oxygen therapy the best option for all patients? Med Clin North Am. 2016;100(5):1123–30.[PubMed]

20. Grieco DL, Menga LS, Eleuteri D, Antonelli M. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. Minerva Anestesiol. 2019;85:1014–23.[PubMed]

21. Solaimanzadeh I. Acetazolamide, nifedipine and phophodiesterase inhibitors: rationale for their utilization as adjunctive countermeasures in the treatment of Coronavirus disease 2019 (COVID-19). Cureus. 2020;12:e7343.[PubMed]

22. Geier MR, Geier DA. Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality. Med Hypotheses. 2020;140:109760.[PubMed]

23. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. N Engl J Med. 1996;334:1642–8.[PubMed]

24. Zhong X, Tao X, Tang Y, Chen R. The outcomes of hyperbaric oxygen therapy to retrieve hypoxemia of severe novel coronavirus pneumonia: first case report. Zhonghua Hanghai Yixue yu Gaoqiya Yixue Zazhi. 2020.

25. Maio AD, Hightower LE. COVID-19, acute respiratory distress syndrome (ARDS), and hyperbaric oxygen therapy (HBOT): what is the link? Cell Stress Chaperones. 2020:1-4.PMC7232923

26. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA. 2020;323:2085-6.PMC7160748

27. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.PMC7270627

28. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan,

China: a descriptive study. Lancet. 2020; 395: 507-13. PMC7135076

29. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–9.PMC7042881

30. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020:1-2. PMC7095524

31. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;181:281-92. [PubMed]

32. Chen I-Y, Chang SC, Wu H-Y, Yu T-C, Wei W-C, Lin S, et al. Upregulation of the chemokine (C-C Motif) ligand 2 via a severe acute respiratory syndrome coronavirus spike-ACE2 signaling pathway. J Virol. 2010;84:7703–12. [PubMed]

33. Liu J, Li S, Liu J, Liang B, Wang X, Li W, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.PMC7165294

34. Wu C, Hu X, Song J, Du C, Xu J, Yang D, et al. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). Vol. 2019, medRxiv. 2020. 2020.02.26.20028589.[FullText]

35. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8:959–70.[PubMed]

36. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004;363(9404):203–9.[FullText]

37. Braunwald E, Sonnenblick EH, Ross J, Braunwald E. Myocardial Oxygen Consumption : The quest for its determinants and some clinical fallout. J Am Coll Cardiol. 2000;35:45B-48B.[ScienceDirect]

38. Heusch G. Myocardial ischemia: Lack of Coronary Blood flow or myocardial oxygen supply/demand imbalance? Circ Res. 2016;119:194–6.[PubMed]

39. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5.[PubMed]

40. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection [Internet]. 2020;(0123456789). DOI https://doi.org/10.1007/s15010-020-01424-5

41. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135:2033-40.[PubMed]

42. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost. 2018;16:231–41.[PubMed]

43. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: Challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood. 2019;133:906–18.[PubMed]

44. Delabranche X, Helms J, Meziani F. Immunohaemostasis: a new view on haemostasis during sepsis. Ann Intensive Care. 2017;7:117.PMC5712298

45. Yang HB, Hu M, Liang JR, Zhang XR, Liu ZG. Microstructure, nano-mechanical and temperature sensitive properties of VOx/porous silicon/Si structure. Acta Phys - Chim Sin. 2008;24(6):1017–22.[Link]

46. Subramaniam S, Jurk K, Hobohm L, Jackel S, Saffarzadeh M, Schwierczek K, et al. Distinct contributions of complement factors to platelet activation and fibrin formation in venous thrombus development. Blood. 2017;129:2291–302.[PubMed]

47. Noubouossie DF, Reeves BN, Strahl BD, Key NS. Neutrophils: back in the thrombosis spotlight. Blood [Internet]. 2019;133:2186—97. DOI https://doi.org/10.1182/blood-2018-10-862243

48. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol. 2008;8:776–87. PMC2786961

49. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417-8. PMC7172722

50. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost. 2019;17:283–94.[PubMed]

51. Saffarzadeh M, Juenemann C, Queisser MA, Lochnit G, Barreto G, Galuska SP, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: A predominant role of histones. PLoS One. 2012;7:e32366. [PubMed]

52. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol. 2003;23:168–75.[PubMed]

53. Xiong M, Liang X, Wei Y. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID□19):

a meta□analysis. Br J Haematol. 2020;189:1050-2. [PubMed]

54. Xie Y, Wang X, Yang P, Zhang S. COVID-19 complicated by acute pulmonary embolism. Radiol Cardiothorac Imaging. 2020;2:e200067.PMC7233431

55. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J Thorac Oncol. 2020;15:700□4.[PubMed]

56. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney impairment is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829-38. [PubMed]

57. Naicker S, Yang C-W, Hwang S-J, Liu B-C, Chen J-H, Jha V. The novel coronavirus 2019 epidemic and kidneys. Kidney Int. 2020;97:824–8.[PubMed]

58. Panitchote A, Mehkri O, Hastings A, Hanane T, Demirjian S, Torbic H, et al. Factors associated with acute kidney injury in acute respiratory distress syndrome. Ann Intensive Care. 2019;9:74.[PubMed]

59. Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med. 2016;194:402–14.[PubMed]

60. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.[PubMed]

61. Pan X-W, Xu D, Zhang H, Zhou W, Wang L-H, Cui X-G. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med. 2020;46:1114-6.[PubMed]

62. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and viral load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. Gastroenterology. 2020;159:81-95.[PubMed]

63. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. bioRxiv. 2020; DOI https://doi.org/10.1101/2020.01.30.927806

64. Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012;487:477–81.[PubMed]

65. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158:1831-3.e3.[PubMed]

66. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol. 2020;18:1561-6.[PubMed]

67. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: A systematic review. Crit Care. 2020;24:421.[PubMed]

68. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995-8. [PubMed]

69. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol. 2018;92:e00404-18.[PubMed]

70. Munster VJ, Prescott JB, Bushmaker T, Long D, Rosen R, Thomas T, et al. Rapid Nipah virus entry into the central nervous system of hamsters via the olfactory route. Sci Rep. 2012;2:736.[PubMed]

71. Brann DH, Tsukahara T, Weinreb C, Logan DW, Datta SR. Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. bioRxiv Prepr. 2020; DOI https://doi.org/10.1101/2020.03.25.009084

72. Cardona GC, Pájaro LDQ, Marzola IDQ, Villegas YR, Salazar LRM. Neurotropism of SARS-CoV 2: Mechanisms and manifestations. J Neurol Sci. 2020;412:116824. [PubMed]

73. Monteleone G, Sarzi-Puttini PC, Ardizzone S. Preventing COVID-19-induced pneumonia with anti-cytokine therapy. Lancet Rheumatol. 2020;2:e255-e256.[PubMed]

74. Jenny NS, Callas PW, Judd SE, McClure LA, Kissela B, Zakai NA, et al. Inflammatory cytokines and ischemic stroke risk: The REGARDS cohort. Neurology. 2019;92:e2375–84.[PubMed]

75. Tsang RS, Valdivieso-Garcia A. Pathogenesis of Guillain-Barré syndrome. Expert Rev Anti Infect Ther. 2003;1:597–608.[PubMed]

76. Hao Y, Wang W, Jacobs BC, Qiao B, Chen M, Liu D, et al. Antecedent infections in Guillain-Barré syndrome: a single-center, prospective study. Ann Clin Transl Neurol. 2019;6:2510–7.[PubMed]

77. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388:717–27.[PubMed]

78. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18-22.[PubMed]

79. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H et al. Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19. N Engl J Med. 2020;382:e38. [PubMed]

80. Mao L, Yanan H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:1-9.[PubMed]

81. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign : Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46:854-87.[PubMed]