Review Article

Systemic manifestations of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), caused due to a novel coronavirus SARS-CoV-2, has swept across the planet and has become a public health emergency of international concern. Like other coronaviruses, it predominantly involves the respiratory system. However, several atypical manifestations of the disease have been reported worldwide in a short span of time. Almost all organ systems (cardiovascular, gastrointestinal, renal, hepatic, endocrine, and nervous system) have been reported to be involved. This review concisely summarizes the systemic effects of COVID-19, thus emphasizing that the disease can present in various forms and the healthcare workers need to be extra vigilant, approaching all patients with a high index of suspicion.

Keywords: Coronavirus, manifestations, nineteen, SARS-CoV-2

Introduction

In December 2019, there was an outbreak of a highly contagious pneumonia in Wuhan city of China, caused due to an enveloped RNA beta coronavirus phylogenetically similar to severe acute respiratory syndrome coronavirus (SARS-CoV), named as SARS-CoV-2.[1] The pneumonia was designated as coronavirus disease 2019 (COVID-19).[2] Although the initial transmission was thought to be zoonotic, it is now spreading from person to person through droplets (directly or through contaminated surfaces) and possibly aerosols with a mean incubation period of 5.2 days.[3,4] SARS-CoV-2 uses the same angiotensin-converting enzyme 2 (ACE2) cell receptor for entry to host cell as was used by SARS-CoV but with significantly enhanced binding affinity due to single mutation in its spike protein.[5]

COVID-19 has been declared as a pandemic by the World Health Organization (WHO) on March 12, 2020. As of June 18, 2020, it has affected 8,489,705 people and caused 452,431 deaths.[6] Patients commonly present with fever, cough, shortness of breath, myalgia, fatigue, and less commonly with sputum production, hemoptysis, headache, and diarrhea.[7-9] Elderly males with comorbidities (diabetes, hypertension, and coronary artery disease) are more likely to be affected[8] as compared to children, who either are not infected are or have only undetectable disease.[10] Leucocyte counts may be normal[11]or low.[8] Lymphopenia is remarkable.[8] Severe disease has increased lactate dehydrogenase (LDH), D-Dimer, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) with normal procalcitonin. COVID-19 involves multiple organ systems and has varied systemic effects [Figure 1].

Systemic Manifestations of COVID-19

Respiratory manifestations

Respiratory system is predominantly involved with manifestations varying from mild flu-such as illness, fulminant

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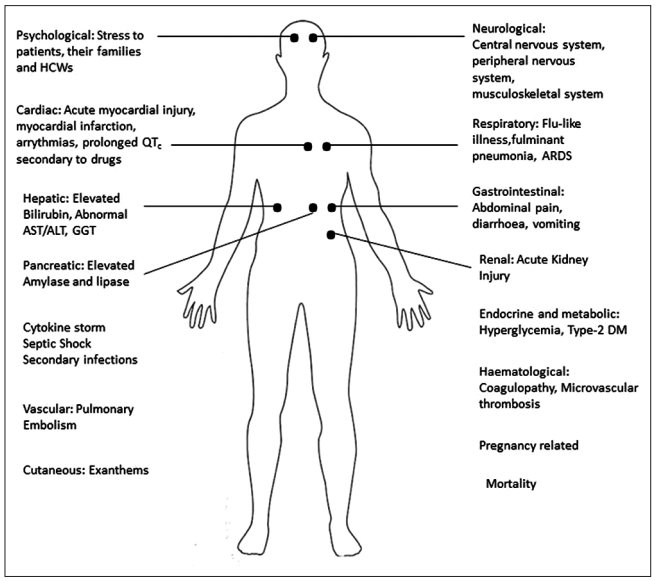

Figure 1: Systemic manifestations of COVID-19

pneumonia to potentially lethal acute respiratory distress syndrome (ARDS).[12] ARDS, clinically diagnosed by Berlin's criteria, commonly develops between 1–2 weeks after symptom onset with reported incidence varying from 17 – 29%.[8,13-15] Chest radiographs in all patients have bilateral infiltrates and common chest computed tomography (CT) findings include ground-glass opacities and consolidation.[16] Diagnosis is done by real-time reverse transcriptase polymerase chain reaction (RT-PCR) of upper and lower respiratory tract secretions.[5]

ARDS occurs either due to virus acting directly through ACE2 receptors in lungs[12] or secondary to cytokine storm.[8] Although postmortem biopsies of COVID-19 lung have revealed viral cytopathic changes with typical ARDS findings (diffuse alveolar damage with hyaline membranes),[17] a study from Italy suggested that COVID-19 pneumonia causes atypical ARDS as lung mechanics are unusually preserved for the degree of hypoxemia.[18] Another distinct mechanism proposed for respiratory failure suggested that some of viral surface proteins and glycoproteins combine with porphyrin to form a complex and several others coordinate to attack the heme on the beta-1 chain of hemoglobin to dissociate iron to form porphyrin. This decreases the capacity of hemoglobin to carry gases and affects gas exchange in the lungs causing intense inflammation and ground-glass-like lung images. Chloroquine could prevent the binding of these surface proteins and glycoproteins to porphyrin and relieve respiratory distress.[19]

ARDS in COVID-19 presents as two different phenotypes. The L-phenotype has lesser lung weight, preserved lung compliance, and hypoxia. Such patients, primarily treated with oxygen, are given high flow nasal cannula, continuous positive airway pressure, or noninvasive ventilation if dyspneic. Once intubated, their compliant lungs can tolerate liberal tidal volume and do not benefit much from high positive end-expiratory pressure (PEEP), recruitment, and proning. Early intubation may prevent progression to H-phenotype which is associated with low compliance, increasing lung weight, and right-to-left shunt. Their lungs are recruitable and they should be treated as conventional ARDS, with high PEEP, prone positioning, and extracorporeal support along with the other evidence-based treatment guidelines for ARDS.[20,21] Although corticosteroids are not recommended routinely, some suggest that their use in early disease may prevent ARDS development.[17,22] The Surviving Sepsis Campaign (SSC) COVID-19 panel has recommended (weak recommendation) the use of systemic steroids in mechanically ventilated patients with respiratory failure due to COVID-19.[22]

Septic shock

Sepsis has been reported in around 60% of patients with COVID-19 and septic shock in 4-20%.[15,23] Sequential Organ Failure Assessment (SOFA) is a good diagnostic marker for sepsis. Pathogenesis possibly is due to the direct involvement of SARS-CoV-2 infection.[15]

Clinical management includes infection prevention and control measures with supportive care. The SSC guidelines propose the use of antimicrobials empirically in patients with respiratory failure on mechanical ventilation, with regular assessment of descalation, along with routine sepsis care as in any other non-COVID patient. The use of antivirals (lopinavir/ritonavir), recombinant interferons, chloroquine/hydroxychloroquine, tocluzimab, immunoglobulins, and convalescent plasma have not been suggested based on insufficient evidence.[22] Guidelines issued by Infectious Diseases Society of America (IDSA) too express that any medical treatment for COVID-19 should be used only in context of clinical trials.[24] In an already conducted trial of 200 hospitalized patients, antiretroviral protease inhibitor lopinavir/ritonavir showed no benefit beyond standard care.[25] Recently, based on two randomized controlled trials (RCTs), the United States Food and Drug Administration (US-FDA) has granted emergency use authorization for use of remdesvir.[26] Clinical trials in China have studied the effectiveness of chloroquine phosphate, an aminoquinoline antimalarial treatment, against COVID-19.[27] Chloroquine increases the endosomal pH making environment unfavorable for the virus/cell fusion and affects the glycosylation process of ACE2.[28,29] However, there is no evidence of improved outcomes.[22,24,29] Even while awaiting the evidence, many clinicians are already using hydroxychloroquine 400-600 mg daily for 5 days treatment of patients with severe COVID-19.[30] Recently, FDA has revoked the

previously granted emergency approval for using chloroquine and hydroxychloroquine in the treatment of COVID-19 in patients outside of the hospital setting or clinical trials due to increased risk of cardiac complications.[31] The Indian Council of Medical Research COVID- 19 National Task Force has advocated extended hydroxychloroquine prophylaxis for selected individuals.A small nonrandomized clinical trial had shown that hydroxychloroquine reinforced by azithromycin significantly reduces viral load COVID-19 patients.[32] However, an observational study of hydroxychloroquine in 1446 hospitalized patients with COVID-19 had failed to demonstrate any significant association between hydroxychloroquine treatment and composite end-point of intubation or death thus emphasizing the need for further trials.[33] Antiparasitic drug Ivermectin has also seen to inhibit SARS-CoV2 *in vitro* and needs further evaluation.[34]

Cytokine storm

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome characterized by a hypercytokinemia with multiorgan failure. Approximately 50% of patients have pulmonary involvement (ARDS) with unremitting fever, cytopenias, and hyperferritinemia. A cytokine profile resembling sHLH (increased interleukin (IL)-2, IL-7, interferon-γ inducible protein 10, granulocyte-colony stimulating factor, tumor necrosis factor-α, monocyte chemoattractant protein 1 and macrophage inflammatory protein 1-α) is associated with severe COVID-19 infection.[35]

Patients with severe COVID-19 should be screened for hyperinflammation (rising ferritin, decreasing platelets, or erythrocyte sedimentation rate) and get HScore (for diagnosis of HLH) calculated to identify patients for whom immunosuppression would reduce mortality. Therapeutic options include steroids, intravenous immunoglobulin, selective cytokine blockade (e.g., anakinra for interleukin-1 or tocilizumab for interleukin-6) and Janus kinase inhibition.[35] It has been suggested that low volume plasma exchange with low dose steroids in sHLH may improve survival.[36] Although SSC guidelines have not supported these treatments, FDA has issued guidance for usage of convalescent plasma in COVID-19 and approved toclizumab for Phase III clinical trial.[22,37,38] Also, several nonrandomized studies have suggested that use of several cytokine adsorption devices to reduce inflammatory cytokine levels and hence their associated complications.[39,40]

Cardiovascular manifestations

Pre-existing cardiovascular disease (CVD) and CV risk factors increase vulnerability to COVID-19. Conversely, COVID-19 can worsen underlying CVD and precipitate new cardiac complications,[12] such as increased risk of acute myocardial injury, myocardial infarction, heart failure and arrhythmias. Postulated mechanisms include direct myocardial injury ((myocardial necrosis, direct myocardial and vascular infections), cytokine storm (causing myocardial depression and plaque rupture), myocardial oxygen supply-demand mismatch (increased demand secondary to sympathetic stimulation and decreased supply because of hypoxia) and hypercoagulabilty.[12,41]

Until a specific therapy for COVID-19 is established, treatment of cardiovascular complications should be based on existing guidelines for CVD with use of antiplatelet agents, ß-blockers, statins, and ACE inhibitors. Immunomodulators by curtailing the hyperinflammatory response may have some role in fulminant myocarditis and ARDS.[41]

Endocrine and metabolic manifestations

Coronavirus attaches to ACE2 cells of pancreas, enters the islets and causes beta-cell dysfunction resulting in hyperglycemia and transient Type-2 Diabetes Mellitus (T2DM). Hypertension and T2DM are the most prevalent comorbidities in patients with severe coronavirus infections. In patients T2DM, increased activation of proinflammatory angiotensin (AT) 1 and AT2 receptor pathways cause increased expression of ACE2 receptor in pancreas and other tissues, leading to higher susceptibility of infection and multiorgan failure. This triggers a dysregulated immune response and excessive cytokine release leading to aggravated lung pathology and tenfold increased risk of death.[42]

Antidiabetic medication (Glucagon-like-peptide-1 agonists) may improve glucose metabolism and blood pressure by improving metabolic function and inducing activity of protective ACE2 and Mas receptor pathways. Competitive binding to ACE2 prevents coronaviruses from entering cells and may restore pulmonary function.[42]

Hematological manifestations

COVID-19 patients have lymphocytopenia, thrombocytopenia, and leukopenia or normal WBC count.[41] Coagulopathy similar to disseminated intravascular coagulation (DIC) is likely in severe disease due to coagulation activation from sepsis, cytokine storm , and impending multi-organ failure.[43]

As in DIC, widespread microvascular thrombosis and consumption of coagulation factors causes thrombocytopenia, prolonged prothrombin time, partial thromboplastin time, elevated D-dimer, and decreased fibrinogen levels. Peripheral smear shows microangiopathy with schistocytes. Elevated D-dimer at admission and increasing D-dimer levels (3- to 4-fold) over time have been associated with high mortality.[43]

For treating coagulopathies, management of underlying condition is paramount. Transfusion is reserved only in cases with active bleeding, requiring an invasive procedure, or patients at high risk for bleeding complications.[43] Early application of anticoagulation with low molecular weight heparin (LMWH) has a better prognosis in severe COVID-19 with markedly elevated D-dimer.[44]

Vascular manifestations

Hypercoagulability, increased microvascular thrombosis, possible epithelial damage, and endothelial dysfunction (as in other influenza pneumonias) along with reduced physical movement due to quarantine requirement can precipitate pulmonary embolism in patients with COVID-19. CT Pulmonary Angiogram facilitates diagnosis when D-Dimer is markedly elevated.[45]

Therapeutic anticoagulation is indicated in documented PE. Prophylactic anticoagulation when given to all hospitalized COVID-19 patients, despite abnormal coagulation tests (in absence of other contraindications active bleeding, and platelet count $<25 \times 109$/L, or fibrinogen <0.5 g/L), may decrease mortality.[43]

Gastrointestinal manifestations

Diarrhea, abdominal pain, and vomiting are seen in 2–10% of patients. The virus nucleic acids can be detected in stools causing likelihood of faeco-oral transmission.[12,46] AT2 receptors are present in stratified epithelial cells of upper esophagus and absorptive enterocytes of ileum and colon. Viral infection increases gastrointestinal wall permeability to foreign pathogens. Enterocyte invasion leads to malabsorption and diarrhea. Accordingly, ACE2 based strategies should be accelerated for diagnosis, prophylaxis, or treatment.[46]

Neurological manifestations

Neurological symptoms of COVID-19 fall into three categories: central nervous system symptoms (headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease including cerebral hemorrhage and infarction, and epilepsy), peripheral nervous system symptoms (hypogeusia, hyposmia, hypopsia, and neuralgia), and skeletal muscular symptoms[47,48] (discussed later). A few cases of acute hemorrhagic encephalopathy, encephalitis, and convulsive seizures have also been reported.[49-51] The expression of ACE2 in the nervous system may contribute to neurological symptoms of COVID-19. Neurological complications are more common with severe disease and neurological involvement carries a poor prognosis.[47]

Musculoskeletal manifestations

Patients have myalgias, fatigue, and elevated creatine kinase levels,[8] probably because of binding of SARS-CoV2 to ACE2 in skeletal muscles or secondary to elevated pro-inflammatory cytokines causing muscle damage.[47] Few cases with rhabdomyolysis have been reported.[8]

Hepatic manifestations

The incidence of liver injury in severe COVID-19 infection is 14.8% to 53%. It manifests as slightly elevated bilirubin, abnormal alanine, and aspartate aminotranferase, elevated gamma-glutamyltransferase, elevated alkaline phosphatase, and hypoalbuminemia.[52,53]

Apart from direct viral infection through ACE2 receptors in liver and bile duct cells and immune-mediated inflammation, pneumonia associated hypoxemia and drugs (lopinavir/ritonavir, antibiotics, steroids) are additional factors contributing to liver injury. Mild liver damage is transient and can be managed conservatively. Interaction between prexisting chronic liver disease and COVID-19 has not yet been studied.[52,54]

Renal and electrolyte disturbances

Acute Kidney Injury (AKI) with COVID-19 infection, is reported to have an incidence of 5-23%[14,55] and in-hospital prevalence of 40%.[55] Patients have proteinuria, hematuria, low glomerular filtration rate, and elevated blood urea nitrogen and serum creatinine levels.[55,56] Computerized tomography (CT) scan of kidneys in affected patients reveal inflammation and edema of renal parenchyma.[56]

The possible mechanisms include dehydration secondary to fever and decreased intake in old persons, hypoxia, hypovolemia, and ischemia leading to tubular necrosis, infection of renal cells by SARS-CoV-2 through ACE2 receptors, cytokine storm syndrome and rhabdomyolysis. Other precipitating factors included presence of uncontrolled diabetes or hypertension and inappropriate use of nonsteroidal anti-inflammatory drugs (NSAIDS).[55,56] Development of renal failure increases risk of in-hospital mortality.[55]

Management is supportive by providing adequate hydration and avoiding nephrotoxic drugs. Dialysis is generally required during second week of infection in around 5% of ICU patients. The choice of modality, hemodialysis (HD) or slow low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT) will depend on patient's hemodynamics, available resources, and local expertise. In view of increasing number of cases, if capacity is exceeded, reducing intermittent HD time to 3 hours, CRRT time to 10 hours with augmented flow rates (40-50 ml/kg/h) or acute peritoneal dialysis have been suggested.[57]

Pregnancy and COVID-19

Pregnant women being immunosuppressed are at high risk of COVID-19 infection. Clinical features in pregnancy are similar to those reported for nonpregnant adults. In addition, it can cause intrauterine growth restriction, miscarriage, preterm delivery, and fetal distress, but it is not transmitted vertically to the fetus.[40,41] Mother-to-child transmission of respiratory viruses mainly occurs through close contact from caregivers.[58]

Mothers having or suspected to have COVID-19 should be carefully monitored before and after delivery. Confirmed cases should be treated with antibiotics and antiviral medication after childbirth. Mothers and neonates should be taken care of in isolated rooms and breastfeeding avoided until infection is ruled out.[59]

Pancreatic manifestations

Pancreatic injury defined by elevation of serum amylase and lipase has been seen in 17% patients. Higher ACE2 expression in pancreatic islets leads to direct cytopathic effect by local SARS-CoV-2 replication cause damage of islets and subsequently acute diabetes. Other suggested mechanisms include systemic responses to respiratory failure or cytokine storm induced by SARS-CoV-2 infection or drug-related pancreatic injury.[53]

Psychosocial issues

COVID-19 pandemic has created enormous psychosocial disturbances. Nonpharmacological interventions to prevent the disease spread (social distancing, lockdowns) has affected millions of lives and economic exchanges. Many problems are being faced by the individuals, healthcare workers, governments, and public health systems:

Individuals

There is a constant worry about own and family's health leading to stress, anxiety, depression, feeling of helplessness, and negative emotions.[60] Economic stress, social isolation, and decreased access to religious support can increase the incidence of suicide.[61] Individuals in quarantine can experience many negative emotions such as anger, confusion, boredom, frustration, lack of supplies, improper information, financial loss, and stigma. People who depend on daily wages for their living long to move back to their native places, as they unable to sustain without any wages, food, and shelter.[62]

Health care workers

The exponential rise in the number of cases has posed a strain on the entire health care system. HCWs are in a state of fear and anxiety. A study showed that excessive workload and working hours, sleep deprivation, lack of essential resources (such as hand sanitizers, N95 masks, personal protective equipments (PPEs), beds, medicines, ventilators), and failure to control the disease has led to burnout in 54.4% of physicians.[63] In worst-affected areas, physicians are having to make the toughest decisions they never before had to face, such as triaging the ventilators, which might expose them to an enormous emotional and spiritual burden.[64] Other issues include facing discrimination in society and being asked to stay away as they are taking care of COVID patients[65] and constant fear of bringing infection home to their families.[65,66] Some feel that it's a suicide mission, so have resorted to writing their wills.[67]

Secondary infections

Secondary infections such as hospital acquired pneumonia, bacteremia and urinary tract infection have been seen in around 10-15% of COVID-19 patients, more so in nonsurvivors than survivors.[8,14,23]

Mortality

The estimated mortality rate in India (3.3%)[68] is almost the same as in the world (3.4%).[6] Case fatality rate is around 2%.[6] The odds of death rise with older age, high SOFA score, and high admission D-dimer levels. Nonsurvivors had a higher rate of comorbidities such as diabetes, hypertension, and coronary heart disease as well as higher laboratory values of troponin, myoglobin, CRP, and inflammatory biomarkers (interleukin-6 and serum ferritin). Nonsurvivors showed higher rates of complications such as respiratory failure, circulatory failure, septic shock and myocardial damage than survivors.[23,69]

Adverse effects of various therapies

Chloroquine interacts with lopinavir/ritonavir, causing prolonged QT interval.[28] Similarly, there is limited data on safety of combination of hydroxychloroquine and azithromycin as both can cause torsade de pointes. Around 460 cardiac arrests have been attributed to chloroquine, hydroxychloroquine, lopinavir/ritonavir, and azithromycin individually. To reduce the risk of torsades and death, cardiac rhythm and QT interval should be regularly monitored during therapy and drugs withheld in patients with QT prolongation (QTc ≥500 msec) or with congenital long QT syndrome. Hypokalemia and hypomagnesemia should be corrected and concomitant use of QTc prolonging agent should be avoided.[70]

Miscellaneous

Electrolyte disturbances

Mild hyponatremia and hypokalemia have been reported,[71] due to the interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system.[71,72]

Cutaneous manifestations

Erythematous rash, widespread urticarial, and chicken-pox such as vesicles mainly involving trunk may be seen.[73]

Late complications

With only few months into the disease, long-term complications among those who survived clinically significant COVID-19 disease are not available yet.[74]

Conclusion

COVID-19 is a highly infectious disease with multitude of effects involving almost all systems of body. It can be life-threatening in elderly patients with multiple comorbidities. In such a short span of time, much has been studied about the disease and research is ongoing for development definite vaccine and treatment of COVID-19. Good quality randomized controlled trials are needed to find definitive treatment. Presently, the focus should be curbing the source of infection and cutting off transmission (hand hygiene, social distancing, avoiding crowded places, patient isolation) and limiting the progress of disease from available resources and supportive care. It can present in various forms and healthcare workers need to be extra vigilant, approaching all patients with a high index of suspicion, taking all precautions.

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Conflicts of interest

There are no conflicts of interest.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. [cited 2020 Apr 12]; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.
3. Yu ITS, Li Y, Wong TW, Tam W, Chan AT, Lee JH, *et al*. Evidence of airborne transmission of the severe acute respiratory syndrome virus. N Engl J Med 2004;350:1731-9.
4. Modes of transmission of virus causing COVID-19: Implications for IPC precaution recommendations [Internet]. [cited 2020 Apr 12]; Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.
5. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91-8.
6. Coronavirus Update (Live): 4,051,326 cases and 277,522 deaths from COVID-19 virus pandemic-Worldometer [Internet]. [cited 2020 May 09]; Available from: https://www.worldometers.info/coronavirus.
7. Henry BM, Vikse J. Clinical characteristics of Covid-19 in China. N Engl J Med 2020;382:1860.
8. 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.
9. Symptoms of Coronavirus | CDC [Internet]. [cited 2020 May 09]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
10. Fauci AS, Lane HC, Redfield RR. Covid-19 - navigating the uncharted. N Engl J Med 2020;382:1268-9.
11. Cao W. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei [Internet]. Infectious Diseases (except HIV/AIDS); 2020 [cited 2020 Apr 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.02.23.20026963.
12. Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr 2020;14:247-50.
13. 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.
14. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *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;8:475-81.
15. 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.
16. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, *et al*. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506-17.
17. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.
18. 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;210:1299-300.
19. Wenzhong L, Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. 2020 [cited 2020 Apr 10]; Available from: https://chemrxiv.org/articles/COVID-19 disease ORF8 and surface glycoproteinn inhibit heme metabolism by binding to porphyrin/11938173.
20. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, *et al*. COVID-19 pneumonia: Different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.
21. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, *et al*. An official American thoracic society/European society of intensive care medicine/society of critical care medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253-63.
22. Alhazzani W, Møller 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;48:e440-69.
23. 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.
24. IDSA COVID-19-gl-tx-and-mgmt-v1.0.3.pdf [Internet]. [cited 2020 Apr 18]; Available from: https://www.idsociety.org/

globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v1.0.3.pdf.
25. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al*. A Trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-99.
26. Commissioner O of the. Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment [Internet]. FDA2020 [cited 2020 May 09]; Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.
27. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases. Lancet Infect Dis 2003;3:722-7.
28. Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): Chloroquine or hydroxychloroquine. Int J Antimicrob Agents 2020;105945. doi: 10.1016/j.ijantimicag. 2020.105945.
29. Sarma P, Prajapat M, Avti P, Kaur H, Kumar S, Medhi B. Therapeutic options for the treatment of 2019-novel coronavirus: An evidence-based approach. Indian J Pharmacol 2020;52:1-5.
30. Gupta N, Agrawal S, Ish P. Chloroquine in COVID-19: The evidence. Monaldi Arch Chest Dis 2020;90. doi: 10.4081/monaldi. 2020.1290.
31. Research C for DE and. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. FDA [Internet] 2020 [cited 2020 Jun 18]; Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting.
32. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949. doi: 10.1016/j.ijantimicag. 2020.105949.
33. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, *et al*. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;382:2411-8.
34. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020;104787. doi: 10.1016/j.antiviral. 2020.104787.
35. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al*. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
36. Alexander V, Zachariah U, Goel A, Kandasamy S, Chacko B, Punitha JV, *et al*. Low-volume plasma exchange and low-dose steroid to treat secondary hemophagocytic lymphohistiocytosis: A potential treatment for severe COVID-19? Curr Med Issues 2020;18:77-82.
37. Research C for BE and Recommendations for investigational COVID-19 convalescent plasma. FDA [Internet] 2020 [cited 2020 Apr 14]; Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma.
38. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol 2020;92:814-8.
39. National Institute for Health and Care Excellence. Cytokine adsorption devices for treating respiratory failure in people with COVID-19. [Internet]. London: NICE; 2020 [published 2020 May 21; cited 2020 Jul 06]. (Medtech innovation briefing [MIB217]). Available from: https://www.nice.org.uk/advice/mib217/chapter/Clinical-and-technical-evidence.
40. Shareef KA, Bakouri M. Cytokine blood filtration responses in COVID-19. Blood Purif 2020. doi: 10.1159/000508278.
41. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: A review. JAMA Cardiol 2020. doi: 10.1001/jamacardio. 2020.1286.
42. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol 2020;16:297-8.
43. COVID-19 and Coagulopathy-Hematology.org [Internet]. [cited 2020 Apr 09]; Available from: https://www.hematology.org: 443/covid-19/covid-19-and-coagulopathy.
44. 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;18:1094-9.
45. Chen J, Wang X, Zhang S, Liu B, Wu X, Wang Y, *et al*. Findings of acute pulmonary embolism in COVID-19 patients [Internet]. Rochester, NY: Social Science Research Network; 2020 [cited 2020 Apr 9]. Available from: https://papers.ssrn.com/abstract=3548771.
46. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020;26:2323-32.
47. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, *et al*. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: A retrospective case series study. medRxiv 2020;2020.02.22.20026500.
48. Wang H-Y, Li X-L, Yan Z-R, Sun X-P, Han J, Zhang B-W. Potential neurological symptoms of COVID-19. Ther Adv Neurol Disord 2020;13:175628642091783.
49. Beijing hospital confirms nervous system infections by novel coronavirus - Xinhua | English.news.cn [Internet]. [cited 2020 Apr 10]; Available from: http://www.xinhuanet.com/english/2020-03/05/c_138846529.htm.
50. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: A case report. Iran Red Crescent Med J 2020;22. Available from: http://ircmj.com/en/articles/102828.html.
51. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiology 2020;201187. doi: 10.1148/radiol. 2020201187.
52. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol 2020;5:428-30.
53. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with COVID-19 pneumonia. Gastroenterology 2020;S0016-5085(20)30409-1.
54. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998-1004.
55. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829-38.
56. Valizadeh R, Baradaran A, Mirzazadeh A, Bhaskar LV. Coronavirus-nephropathy; renal involvement in COVID-19. J Renal Inj Prev 2020;9:e18.
57. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: Our experience from seattle. Am J Kidney Dis 2020;76:4-6.
58. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia [Internet]. [cited 2020 Apr 18]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7036645.
59. Panahi L, Amiri M, Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy; a narrative review. Arch Acad

Emerg Med 2020;8:e34.
60. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, *et al*. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020;17:1729.
61. Suicide Mortality and Coronavirus Disease 2019—A Perfect Storm? | Infectious Diseases | JAMA Psychiatry | JAMA Network [Internet]. [cited 2020 Apr 16]; Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2764584.
62. Revised Psychosocial issues of migrants COVID19.pdf [Internet]. [cited 2020 Apr 16]; Available from: https://www.mohfw.gov.in/pdf/RevisedPsychosocialissuesofmigrantsCOVID19.pdf.
63. Shah K, Chaudhari G, Kamrai D, Lail A, Patel RS, KS, *et al*. How essential is to focus on physicians health and burnout in coronavirus (COVID-19) pandemic? Cureus J Med Sci 2020;12:e7538.
64. Truog RD, Mitchell C, Daley GQ. The toughest triage — allocating ventilators in a pandemic. N Engl J Med 2020;382:1973-5.
65. Doctors, nurses face stigma over coronavirus, asked to vacate rented homes [Internet]. [cited 2020 Apr 16]; Available from: https://www.livemint.com/news/india/doctors-nurses-face-stigma-over-coronavirus-asked-to-vacate-rented-homes-11585074366997.html.
66. Doctors Fear Bringing Coronavirus Home: 'I Am Sort of a Pariah in My Family' - The New York Times [Internet]. [cited 2020 Apr 16]; Available from: https://www.nytimes.com/2020/03/16/us/coronavirus-doctors-nurses.html.
67. Physician Couples Draft Wills, Face Tough Questions Amid COVID-19 [Internet]. [cited 2020 Apr 16]; Available from: https://www.medscape.com/viewarticle/927805.
68. India's Covid-19 Death Toll Near 12,000-Mark: In Charts [Internet]. [cited 2020 Jun 18]; Available from: https://www.bloombergquint.com/coronavirus-outbreak/indias-covid-19-death-toll-at-nearly-12000-mark-in-charts.
69. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846-8.
70. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in exploratory COVID-19 (Coronavirus Disease 2019) treatment. Heart Rhythm 2020;141:e906-7.
71. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, *et al*. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623. doi: 10.1016/j.tmaid. 2020.101623.
72. Chen D, Li X, Song Q, Hu C, Su F, Dai J. Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). medRxiv 2020. doi: 10.1101/2020.02.27.20028530.
73. Recalcati S. Cutaneous manifestations in COVID-19: A first perspective. J Eur Acad Dermatol Venereol 2020;34:e212-3.
74. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19) [Internet]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Apr 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776.