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Effects on cardiovascular disease associated with COVID-19: A Review

Short title: CVD associated with COVID-19

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ABSTRACT

Coronavirus disease (COVID-19) epidemic caused by severe acute respiratory syndrome coronavirus 2 has been declared an international public health emergency. COVID-19 may affect people with cardiovascular disease (CVD) at high risk for adverse effects, and infection alone is associated with cardiovascular complications. COVID-19 can manifest as an acute respiratory distress syndrome in serious cases and the most vulnerable identified in patients with pre-existing cardiovascular co-morbidities. Cardiac complication including arrhythmias, acute myocardial injury, cardiogenic shock, is often found in serious cases and closely correlated with mortality. A substantial number of patients with COVID-19 have chronic CVD and/or heart risk factors. The co-morbidity in COVID-19 patients with predecessors severe acute respiratory syndrome coronavirus 2 and middle-east respiratory syndrome associated with CVD. To provide effective medical services for critically ill patients, recognizing the impact of COVID-19 on the cardiovascular system is therefore necessary. In this review, we tried to summarize the rapidly changing evidence and highlight the cardiovascular considerations associated with COVID-19.

Keywords: Cardiovascular diseases; COVID-19; severe acute respiratory syndrome coronavirus 2

INTRODUCTION

Coronavirus disease (COVID-19) are single-stranded positive-sense RNA viruses, with the capacity for rapid mutation and recombination.(1) COVID-19 infected pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in 2002 and middle-east respiratory syndrome (MERS) in 2012.(2) Previous studies have noted cardiac arrhythmias, cardiomyopathy, and cardiac arrest as life-threatening events in patients with SARS-CoV-2 and MERS.(3, 4) Also, a large proportion of COVID-19 patients have underlying cardiovascular diseases (CVD) and/or cardiac risk factors.

COVID-19 patients with pre-existing CVD have been confirmed to be at high risk for adverse effects, and infection alone is associated with cardiovascular complications.(5) This review was performed to understand the potential effects on the cardiovascular system considerations associated with COVID-19.

PATHOPHYSIOLOGY OF SARSCOV-2

SARS-CoV-2 was initially detected in Wuhan from the Chinese city in December 2019.(6) SARS-CoV-2 is an enveloped virus with a single-stranded and positive-sense RNA virus.(7, 8) It resembles MERS-CoV (around 50% nucleotide identity) and SARS-CoV.(9) The virus is transmitted primarily from human to human by respiratory droplets formed by an infected person.(10)

Previous studies demonstrated that SARS-CoV-2 belongs to ß corona-virus (CoeV) and binds its viral spike (S) proteins to zinc peptidase angiotensin-converting enzyme 2 (ACE2) proteins for cell entry.(11, 12) Four structural proteins contain vital role in COVID-19, namely spike, envelope, membrane, and nucleocapsid proteins of which spike protein arbitrates the viral entrance into host cells. The virus shows strong binding to soluble angiotensin-converting enzyme (ACE) 2 receptors and cell-associated articulated in several organs such as the kidneys, lung, heart, brain, liver, and intestine.(13) COVID-19 particles have been observed at the bronchiolar mucosa in ciliated columnar epithelial cells.(14) (**Table 1**)

After gaining entry into the cells via ACE2 receptors, SARS-CoV-2 down-regulates the expression of ACE2 such that the enzyme is unable to exert on various organs protective effects.(15) ACE2 is highly expressed in alveolar lung cells and plays a role in the lungs; thus, viral binding to this receptor deregulates the lung pathway, which contributes to viral pathogenicity.(16) **Figure 1** shown the pathological changes in COVID-19.

PRE-EXISTING CARDIOVASCULAR DISEASE PATIENTS

According to the latest coronavirus Infection pneumonitis diagnosis and treatment protocol (Trial Version 4), older people are more likely to become infected with SARS-CoV-2, including hypertension, diabetes or CVD. Hence, patients with CVD account for a substantial proportion of death due to COVID-19.(17) In one study, 11.3% of the patients with COVID-19 had coronary artery disease, 2.1% had a history of congestive heart failure, and 3.4% had a history of cardiac arrhythmia.(18) Another study involved 1,099 confirmed COVID-19 patients, 15.74% had a serious illness, with co-morbidities of 23.7% were hypertensives, 5.8% had coronary heart disease (CHD), and 2.3% had a cerebrovascular disorder.(19) Furthermore, SARS-CoV-2 affected have more systemic effects and severe pneumonia in patients with greater than 60 years of aged.(20) Most recently, results from 22,512 COVID-19 patients in the Italian population found that 1.5% patients died in the cohort, 30% had an ischemic heart disease, 24.5% had atrial fibrillation, and 9.6% had ischemic heart disease.(21) In the analysis of 44,672 confirmed COVID-19 cases from Wuhan, China was noted increased case fatality rates in patients with 10.5% CVD, 7.3% diabetes, and 6.0% hypertensive, all markedly higher than the 2.3% overall case fatality rate.(21) Thus, underlying CVD can exacerbate pneumonia and increase the severity of symptoms in patients with SARS-CoV-2 infection.

At present, the mechanism remains unclear for these associations. Potential explanations include CVD being more prevalent in those with advancing age, a functionally impaired immune system, increased levels of ACE2, or a predisposition to COVID-19 for those with CVD. The possible causes include CVD more prevalent in those with advancing age, a functionally impaired immune system, elevated ACE2 levels, or a predisposition to COVID-19.(22)

CARDIOVASCULAR INDICATION OF COVID-19

Previously reported studies postulated one of the identified and common co-morbidity in patients with COVID-19 predecessors SARS-CoV-2 and MERS associated with CVD. In SARS incidence of co-morbidities such as Diabetes mellitus and CVD were 11% and 8% respectively and risk of death raised by 12-fold by the existence of any co-morbidity raised. Diabetes and hypertension were prevalent in 50% of MERS identified cases. As previous studies reviled that as total co-morbid cases, CVD was present in 30% of patients.(22)

Those patients suffering from diseases were more severe with COVID-19 infection, there is an increased presence of comorbidities such CVD. In support to this one reported oversighting in one of the setup from Wuhan, China with 191 COVID-19 patients postulated that among these, 48% had co-morbidities out of that non-survivors 67%, in case of hypertension it was observed 30% survivors and 48% of non-survivors, for diabetes it was 19% (31% of non-survivors), and CVD in 8% (13% of non-survivors).(5) In another similar observation, co-morbidities in a cohort of 138 COVID-19 hospitalized patients was observed that as result of cardiovascular co-morbidities 46% overall and 72% in patients needing intensive care unit (ICU) care, whereas in case of hypertension 31% (58% in patients who required ICU support), 15% CVD (25% in patients who required ICU support), and 10% diabetes (22% in patients who required ICU support).(17) Data from China's National Health Commission found that 35% of COVID-19-diagnosed patients were hypertensive and 17% had CHD.(23) The recent meta-analysis of eights reports from China involving 46,248 contaminated patients revealed uncertain mechanism involved in the pathogenesis, the most prevalent co-morbidities were hypertension (17 ± 7, 95% CI 14-22%), diabetes (8 ± 6, 95% CI 6-11%) and followed by cardiovascular disease (5 ± 4, 95% CI 4-7%).(24) Potential causes include CVDs that are more common in older patients, a functionally compromised immune system, or elevated ACE2 levels, or CVD patients with COVID-19 predisposition.(25)

MYOCARDIAL INJURY

SARS-CoV-2 has pathogenicity, which enhances the myocardial damage caused by this viral infection. Elevated cardiac biomarkers observed with moderate to severe cases of COVID-19 patients. As mentioned earlier sample of 138 hospitalized patients in Wuhan provenience of China out of that 7.2% overall patients and 22% of ICU based patient developed cardiac injury associated with very high levels of biomarkers such as cardiac troponin I (hs-cTnI), as well as changes in echocardiographic abnormalities, were observed.(17) In another set of observations, five patients out of the first 41 patients developed myocardial damage with very high levels (>28 pg /mL) hs-cTnI.(26) In separate group studies, a meta-analysis of 1527, COVID-19 patients in six trials revealed that acute myocardial associated injury was at least 8% of total patients.(27) China's National Health Commission survey indicated that about 12% patients with no previous history of CVD had a remarkable rise in the levels of troponin associated with promising incidences of cardiac arrest at the time of hospitalization.(16)

Remarkably, as compared to 1% of survivors with 46% of non-survivors the levels of a hs-cTnI greater 99th percentile upper reference limit.(22) There are two identified trends of myocardial injury in a patient with early findings of COVID-19 infection. In one of the analysis, it observed that in non-survivors, the median hscTnI values were 8.8 pg/mL as compared to survivors, which had 2.5 pg/mL levels after day four onset of symptom. In observation, there is no improvement in the levels of median hscTnI among survivors. During follow-up period on seven days of treatment the levels was 2.5 to 4.4 pg/mL, while on 13th day the level was raised up to 55.7 pg/mL sequentially on 19th day it was 134.5 pg/mL and reached up to 290.6 pg/mL on 22nd day in non-survivors cases.(5)

The increased risk of myocardial injury associated with the spike in hs-cTnI tracks and formation of inflammatory biomarkers such as interleukin-6, D-dimer, lactate dehydrogenase and ferritin. The precise process for involving COVID-19 in CVD is still under study. Direct myocardial activity mediated by ACE2 is one possible pathway.(28) Several studies reported that in the case of SARS-CoV-2, there is an occurrence of acute myocardial injury as a result of severity disease that brings out through viral myocardium infection, systemic inflammation and cytokine storms.(29-33) Latest retrospective findings have shown that acute myocardial damage is a frequent occurrence in COVID-19 patients and is correlated with the seriousness of the disorder and mortality.(26, 34)

NEW-ONSET HEART FAILURE

The new-onset and prevalence of heart failure in between survivors and non-survivors of COVID-19 infection postulated that prevalence in non-survivors nearly to 23% and estimated to be more as compared to survivors.(5) One of the previously reports highlighted that in case of underlying CVD associated with COVID-19 infection leads to a clinical condition like acute heart failure and may result in cardiac shock. Controlling parameters may efficiently involve use of invasive tech like pulmonary artery catherization as procedural part for hemodynamic testing as preventing measure for controlling the cardiac portion.(35)

CARDIAC ARRHYTHMIA

Earlier reported COVID-19 studies in 138 hospitalized patients recorded 16.7% cases of cardiac arrhythmia in ICU Patients.(17) Guo et al., in one of his study reported on COVID-19 patients highlighted that increased the incidences for ventricular fibrillation and tachycardia with myocardial damage was compared to those without myocardial injury, indicating a

promising relationship of cardiac activity with arrhythmias.(36) Seecheran et al. reported that Caribbean-Black middle-aged COVID-19 patient with initially atrial flutter with two to one atrioventricular block and transitioned to atrial fibrillation.(37) Simultaneously, increasing evidence of arrhythmia in patients with severe disease because of metabolic hypoxemia, neurohormonal or dysfunction, or inflammatory load in the presence of viral infection.(7)

VENOUS THROMBOEMBOLISM

A noxious complication as blood clotting and formation of coagulopathy was observed as a severe and critical complication in a patient with COVID-19. Zhou et al. successfully suggested that the thrombus formation may be associated with the increased mortality rate in most severe cases of COVID-19.(5) In one of the identified pathways for the pathogenesis of acute form of COVID-19 which is responsible for the evaluation of blood coagulation mainly includes increased thrombosis load on chemokine release or pro-inflammatory cytokine, endothelial dysfunction or damage, with possibilities for coagulopathy results of sepsis.(38) Recently reported study reveals that severe lung inflammation with decrease exchange of pulmonary gases in case of COVID-19 has been associated with enhanced endothelial dysfunction and pro-inflammatory cytokine release upregulation.(31) The venous thromboembolism incidence remains unknown, and it probably due to the lack of systematic imaging or asymptomatic presentation.(39)

DRUG THERAPY AND COVID-19

The clinical symptoms and adverse event associated with the use of medication in COVID-19 bring the attention of healthcare professional while giving care to the patients. The implication of various agents such as antivirals, immunomodulators and antimalarial along with plasma and glucocorticoids from recovered donors in the treatment of COVID-19 showed variable outcomes. Drugs like hydroxychloroquine and chloroquine reported causing glycosylation of ACE2 receptors, which is an important tool for the COVID-19 assessment.(16) At present, no precise drug therapy exists is not available for the management of COVID-19. However, numbers of trials are underway to develop drug therapy and vaccination to control COVID-19. (39)

CONSEQUENCE OF COVID-19 PATIENTS WITH CARDIOVASCULAR DISEASE COMORBIDITY

In the present discussion, the number of reported studies highlighted the in-depth relationship between co-morbidities of CVD and serious stages of COVID-19 infections.(40-43)

It is believed that COVID-19 reactions can be traced to an extreme immune reaction in which the body releases the cytokine storm, as a consequence of SARS-CoV-2 infection may be responsible for the severe respiratory distress. Many of the critical COVID-19 cases with multiple complications have been found to be closely associated with cytokine storms. This included probable causes of ischemic heart disease, shock and other organ failures. (44)

It is likely to be noted that case fatality ratio (CFR) is one of the essential factor and based upon the age when require to be revealed in case of co-morbidities. On the practical consideration, CFR is likely to be less than 1% among the population aged below 50 years, approximately 1.3% among the patients average aged between 50 to 59 years, for the age of patients between 60 to 69 years it is likely to be 3.6%, between old group 70 to 79 it is 8% and more than 14% for those aged more 80 years.(45)

Although proof at the specific effects of COVID-19 associated with CVD remains slightly recognised, apart from there are reports of acute cardiac damage, arrhythmias, tachycardia, and an excessive burden of concomitant CVD in inflamed individuals, especially in patients with better co-morbidities and risk elements who require more intensive care. Furthermore, in comparison with sufferers without co-morbidities, in whom the CFR is 0.9 percentage, sufferers with clinical co-morbidities have a notably multiplied CFR: 10.5% for CVD, 7.3% for diabetes mellitus, 6.3% for persistent obstructive pulmonary disorder, 6% for high blood pressure, and 5.6% percentage for most cancers.(45)

CONCLUSION

Cardiovascular co-morbidities are mostly being occurred in patients with COVID-19 associated with increased risk for morbidity and mortality. Similarly, pre-existing chronic disease condition such as hypertension and diabetes also has a strong contributing factor for developing cardiovascular event. Age factor had a higher risk for CVD, and its impact on the immune system may be very significant in understanding COVID-19 severity. The mechanism of these correlations remains uncertain. COVID-19 is predominantly a respiratory illness, a number of patients with pre-existing CVD or underlying new-onset cardiac failure seem to be susceptible to myocardial injury. In patients with increasing age and compromised immune system, higher levels of ACE2, or a predisposition to COVID-19 for those with CVD, possible causes include CVD being more predominant. Centered on the evident that

SARS-CoV-2 virus can affect the cardiovascular system, during the treatment of COVID-19, precise consideration must be paid to cardiovascular protection and functional restoring.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES

1. Pal M, Berhanu G, Desalegn C, Kandi V. Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2): An update. Cureus. 2020;12(3).
2. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol. 2020.
3. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25(6):291-4.
4. 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.
5. 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. The lancet. 2020.
6. 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.
7. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol. 2020;75(18):2352-71.
8. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502.
9. 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. The Lancet. 2020;395(10224):565-74.
10. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environmental research. 2020;188:109819.
11. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
12. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020.
13. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17(6):613-20.

14. Yao X, Li T, He Z, Ping Y, Liu H, Yu S, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua bing li xue za zhi= Chinese journal of pathology. 2020;49:E009-E.
15. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382(17):1653-9.
16. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46(4):586-90.
17. 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(11):1061-9.
18. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med. 2020.
19. 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(18):1708-20.
20. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395(10223):514-23.
21. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323(18):1775-6.
22. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation. 2020;141(20):1648-55.
23. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259-60.
24. Flaherty GT, Hession P, Liew CH, Lim BCW, Leong TK, Lim V, et al. COVID-19 in adult patients with pre-existing chronic cardiac, respiratory and metabolic disease: a critical literature review with clinical recommendations. Tropical Diseases, Travel Medicine and Vaccines. 2020;6(1):1-13.
25. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020.
26. 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. The lancet. 2020;395(10223):497-506.
27. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531-8.
28. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J. 2020.
29. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann Saudi Med. 2016;36(1):78-80.
30. Hui H, Zhang Y, Yang X, Wang X, He B, Li L, et al. Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia. MedRxiv. 2020.
31. Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020.
32. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020.

33. Meyer P, Degrauwe S, Van Delden C, Ghadri J-R, Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. Eur Heart J. 2020;41(19):1860-.
34. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA cardiology. 2020.
35. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, et al. The variety of cardiovascular presentations of COVID-19. Circulation. 2020.
36. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA cardiology. 2020.
37. Seecheran R, Narayansingh R, Giddings S, Rampaul M, Furlonge K, Abdool K, et al. Atrial Arrhythmias in a Patient Presenting With Coronavirus Disease-2019 (COVID-19) Infection. Journal of investigative medicine high impact case reports. 2020;8:2324709620925571.
38. Alosaimi B, Hamed ME, Naeem A, Alsharef AA, AlQahtani SY, AlDosari KM, et al. MERS-CoV infection is associated with downregulation of genes encoding Th1 and Th2 cytokines/chemokines and elevated inflammatory innate immune response in the lower respiratory tract. Cytokine. 2020;126:154895.
39. Matsushita K, Marchandot B, Jesel L, Ohlmann P, Morel O. Impact of COVID-19 on the Cardiovascular System: A Review. Journal of clinical medicine. 2020;9(5).
40. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, et al. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. Curr Probl Cardiol. 2020:100617.
41. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLoS One. 2020;15(8):e0238215.
42. Bansal M. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020.
43. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nature Reviews Cardiology. 2020:1-16.
44. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. The Journal of clinical investigation. 2020;130(5):2202-5.
45. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
46. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. The Lancet. 2020;395(10223):473-5.
47. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clinical Infectious Diseases. 2020.
48. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020.

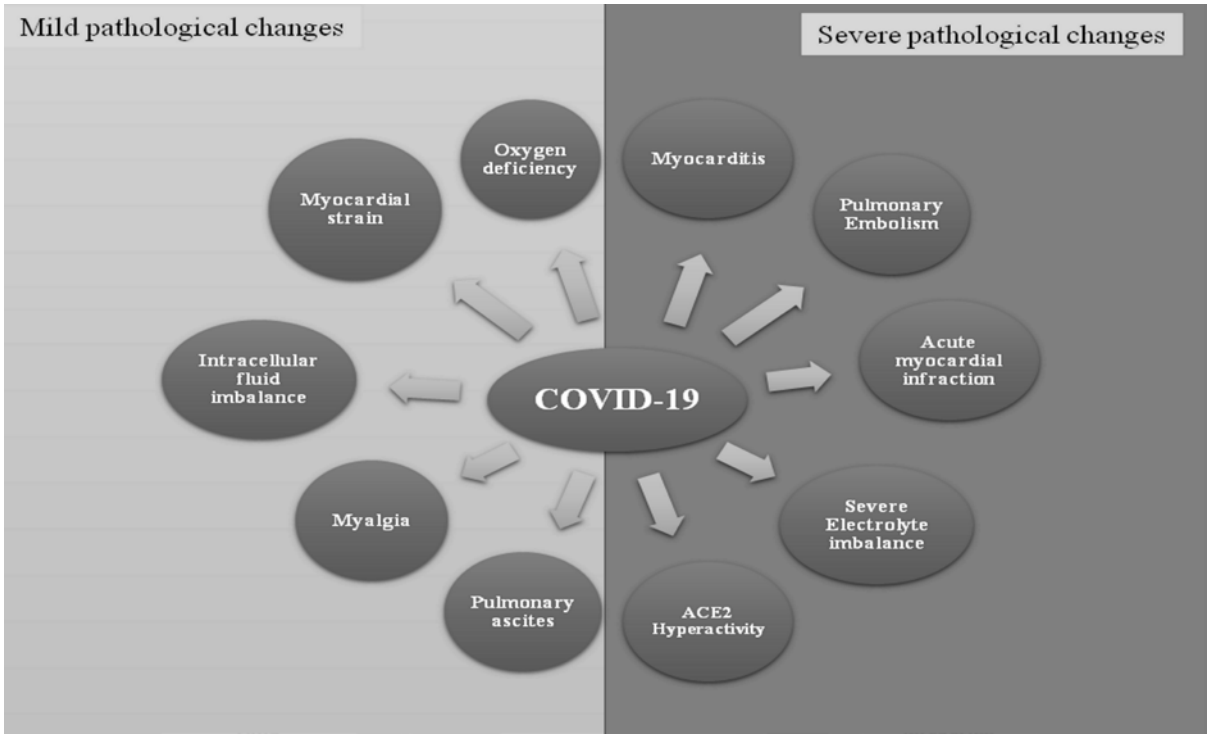

Figure 1: Pathological changes in COVID-19

Table 1: COVID-19 Infection Stages

Stages	Description	Aetiopathogenosis	Pathological Changes	Clinical Symptoms	Therapeutic Strategies	References
1	Stage of viral inoculation	Initial stage of infection where occurred due to viral response	Increased levels of IL6, LDH, D dimer, PT, CRP; ferritin; Moderate changes associated with leukopenia, lymphopenia. Procalcitonin may be normal	Involvement of Gastrointestinal system and respiratory system including symptoms like malaise, fever, and a dry cough and abdominal distress	Therapeutic Strategies mainly includes use of Antimicrobial agents and antiviral drugs like remdesivir proven to beneficial for reducing symptoms	Wan Y et al (45). 2020
2	Stage of viral replication	Virus targeting lungs results in inflammation, pulmonary phase and pulmonary pneumonia	In stage II of infection CT Scan scoring of patient reveled the remarkable changes in chest parameters along with elevated levels of inflammatory and cardiac biomarkers (Troponin, BNP)	Clinical Symptoms includes a viral pneumonia, with cough, fever, and possibly hypoxia and Shortness of PaO2/FiO2 ratio will be less 300	Supportive care including use of antiviral agent and restricted IV fluid therapy and oxygen monitoring	Russell CD et al (46). 2020
3	Stage of severe illness	In this stage of infection patient develop severe symptoms specifically an Extrapulmonary systemic hyper inflammation syndrome	In stage II of infection cardiac cytokine biomarkers such as IL-2, IL-6, IL-7 along with tumor necrosis factor will be remarkably increased	ARDS SIRS, sepsis cardiac failure multi organ dysfunction, DIC, shock	Supportive care including vasoactive drips if indicated along with use of immunomodulatory agents and use of corticosteroid will be justifiable	Qin C et al (47). 2020 and Wu C et al (48). 2020

ARDS: acute respiratory distress syndrome, CRP: C reactive protein, CT: computed tomography, DIC: disseminated intravascular coagulation, ID: infectious disease, IL6: interleukin 6, IV: intravenous, LDH: lactate dehydrogenase, PT: prothrombin time, SISI: systemic inflammatory response syndrome.