



A BRIEF REPORT ON COMORBIDITIES AND RISK FACTORS OF COVID-19 (SARS-COV-2) PATIENTS

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ABSTRACT

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) caused over 3 million infections and over 250,000 deaths worldwide 2 months after the World Health Organization declared the virus-induced disease a pandemic. Certain comorbidities and risk factors have shown increased susceptibility and disease severity. Earlier reports suggested that elderly patients with comorbidities, particularly diabetes, cardiovascular disease, renal insufficiency, obesity and hypertension, suffered greater mortality than younger patients. In addition to the comorbidities, there are certain risk factors (age, sex, race, ethnicity and genetics) which further deteriorate the condition of Covid-19 patients. Hence a review of literature on the impact of comorbidities and risk factors on Coronavirus 2 was of profound interest. An electronic search was conducted in Lit Covid, PubMed, Google Scholar, WHO, and Centers for Disease Control and Prevention databases. Search terms included COVID-19, SARS-CoV-2, comorbidities and risk factors. Manuscripts published were reviewed; relevant references were checked before making this report on the comorbidities and risk factors of Covid-19.

KEYWORDS: Coronavirus 2, Comorbidities, Cardiovascular, Diabetes, Neurology, Renal insufficiency, Risk factors.

INTRODUCTION

On March 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic, and the reality of the situation has finally caught up to the widespread reach of the disease. While coronavirus disease (COVID-19) is not the first global pandemic of the 21st century^[1], it has generated unprecedented complexity, in addition to global concern and responses. COVID-19, caused by severe acute respiratory syndrome (SARS-CoV-2), is thought to have emerged from a zoonotic source. Pandemics in the past have emerged from natural transmission through animals, known as zoonotic transmission, and it often takes months or years to discover the host that the virus passed through as it adapted to infect humans. In some cases, as in Ebola, the original natural source has never been identified.^[2] and spread rapidly in humans through respiratory droplets and contact.

Covid comorbidities

Comorbidity is the simultaneous presence of two or more diseases or medical conditions in a patient. Since the emergence and global transmission of the SARS-CoV-2 virus, many studies have reported that several underlying

medical conditions among adults, are cardiovascular disease, diabetes, renal, lung, neurological and hepatic diseases. These are the primary comorbidities, which have been reported to be associated with increased risk for severe illness from COVID-19. The risk factors of age, sex, and race/genetics had limited-to-moderate evidence. Patients with these comorbidities and risk factors have severe responses to the coronavirus infection.^[3-5]

The presentation of the disease is highly variable, ranging from asymptomatic carriers to critical COVID-19. The availability of angiotensin-converting enzyme 2 (ACE2) receptors may reportedly increase the susceptibility and/or disease progression of COVID-19. Comorbidities and risk factors have also been noted to increase COVID-19 susceptibility. Here, we hereby review the evidence pertaining to ACE2's relationship to common comorbidities, risk factors, and therapies associated with the susceptibility and severity of COVID-19.

Cardiovascular Diseases

Heart disease is the leading cause of death in the United States, causing about 1 in 4 deaths. This brief report will

provide a focused overview of cardiovascular complications associated with COVID-19, including myocardial injury and myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events. The damage caused by SARS-CoV-2 to the cardiovascular system cannot be disregarded. Several pathological and clinical factors such as hypoxemia, excessive proinflammatory cytokines, oxidative stress, and even the medicines used in treatment appear to be responsible for the cardiovascular complications in COVID-19 patients, and all these factors can act upon one another to deteriorate the tissue damage. It would help COVID-19 patients to be able to determine the mechanisms accounting for the untoward medical occurrence in the cardiovascular system to improve the prognosis, specifically for those patients with underlying cardiovascular disease. Huang et al found that about 12% of patients with COVID-19 were diagnosed with acute myocardial injury.^[3,6] In another longitudinal study of patients with confirmed COVID-19, cardiac injury occurred in 19.7%, and it has become an independent risk factor for in-hospital mortality.^[4,7] A study of patients with severe COVID-19 found that 58% had hypertension, 25% had heart disease, and 44% had arrhythmia.^[5,8] Ruan et al identified clinical predictors of mild and serious patient outcomes based on an analysis of 150 patients from Wuhan, China. They noted that cardiovascular disease patients have an increased risk of death when they are infected with SARS-CoV-2 ($P < 0.001$).^[6,9] A summary of 44 672 COVID-19 cases documented by the Chinese Center for Disease Control and Prevention demonstrated a case fatality rate of 10.5% with comorbid CVD, compared to a 2.4% overall case fatality rate.^[7,10]

Hypertension

This is a remarkable risk factor for escalated morbidity and mortality from COVID-19^[11], but whether hypertensive individuals are more susceptible to infection is not clear^[12]. Hypertension prevalence in COVID-19 patients seen in a meta-analysis denotes 21.1% (13.0–27.2).^[11] Furthermore, a ratio of the hazard rate (1.7–3.05) was reported for mortality in COVID-19 patients with hypertension.^[13] SARS-CoV-2 predisposition may be due to ACE2 polymorphisms in individuals with hypertension.^[14] Experimental models have solidified ACE2 as a protector against hypertension.^[15] A necropsy study of 20 patients diagnosed with hypertensive cardiomyopathy or nephropathy showed reduced local ACE2 expression.^[16] However, human and animal models positively correlate the activity of ACE2 in plasma with increased systolic blood pressure.^[17] Li et al.^[18], determined higher serum ACE2 concentrations in hypertensive patients as compared to healthy subjects. Another study revealed that ACE2 activity was 1.5 times greater in 239 hypertensive patients than in healthy volunteers.^[17] No association between plasma ACE2 and hypertension was reported in other studies.^[19] It is not clear, whether SARS-CoV-2 utilizes plasma ACE2 as an active domain

to replicate, but ACE2 shedding amplifies endothelial dysfunction and hyperinflammation, thus potentially increasing COVID-19 severity. Experimental studies and pathological reports clearly find a decrease in local tissue ACE2 activity, which may relate to progressive organ damage from hypertension. However, strong evidence suggests associations between hypertension and elevated plasma ACE2 and upregulation of ADAM17, which may increase COVID-19 severity in hypertensive patients.^[20]

Endocrinological Disorders

Type II diabetes mellitus (T2D) and obesity (body mass index ≥ 30) patients are evidently at high risk of COVID-19 susceptibility and severity^[21,22], while evidence for risk in type I diabetes mellitus is limited.^[21,22] Many blood sugar controlling organs are rich in ACE2.^[23] Aside from diabetic nephropathy modulating ACE2 expression as mentioned, pancreatic islet cells reportedly have elevated enzyme expression and have been postulated as a target for SARS-CoV-2 infection.^[24] Thus, pancreatic viral toxicity potentially explains for new-onset diabetes or worsening metabolic control in patients with diabetes.^[25]

One study determined the pathogenesis of increased glucose to directly increase viral load, ACE2, and IL-1 β expression in SARS-CoV-2-infected monocytes in a dose-dependent manner. Subsequent treatment with glycolysis inhibitors completely inhibited viral replication in infected monocytes and decreased ACE2 and IL-1B expression.^[26] While pathophysiology in increased risk of worse outcomes in diabetics is most likely multifactorial, obesity has strong associations to T2D and increased risk to COVID-19 susceptibility and severity.^[21,26] Of 257 critically ill patients hospitalized in New York City, 36% were diabetic, 46% obese.^[27] Pooled analysis from 75 studies found that obese individuals were more at risk for COVID-19.^[28,29]

Pulmonary disease

Gordon et al.^[30] recently identified 26 of the 29 SARS-CoV-2 proteins that bind to 332 human proteins and hijack the host translational machinery. Renin-angiotensin system (RAS) activity is intrinsically high in the lungs. Histopathological reports acknowledge direct viral toxicity, resulting in atypical cells and detaching II pneumocytes, hyaline membrane formation, interstitial inflammatory response, and endothelial dysfunction.^[31] A pathophysiology of 65 cases emphasized direct lung damage from viral organotropism during the first week but later transitioned to host inflammatory and hypercoagulable responses 10–28 days into the disease phase.^[32] Reports show mainly bronchitis and pneumonitis in mild/moderate individuals and pneumonia, acute respiratory distress syndrome, and pulmonary embolism in severe/critical patients.^[32]

ACE2 elevation exists in acute and chronic lung disease to prevent lung injury. A study on the previous SARS-CoV virus revealed it in autopsy specimens from severe

SARS patients with an elevated ACE2, SARS-CoV S protein, RNA, and proinflammatory cytokines.^[33] Chronic lung disease studies have pursued ACE2's role in chronic obstructive pulmonary disease, emphysema, asthma, and other ailments.

Neurological disease

Ramani *et al.*^[34] have revealed that SARS-CoV-2 readily targets cortical neuronal cells and induces tauopathies and neuronal cell death.

The other study by Song *et al.*^[35] models the SARS-CoV-2 infection of neuronal cells in hiPSC-derived brain 3D organoids. These comorbidities thus lead to higher risk of disease development and higher mortality associated with COVID-19. It is largely assumed that other neurological manifestations will likely surface in the near future.

Hepatic disorder

At least 7 relatively large-scale case studies from China have reported the clinical features of patients with COVID-19.^[36-38] These data indicate that 2–11% of patients with COVID-19 had pre-existing liver diseases. Recently, Grasselli *et al.*,^[39] reported that, among the first 1,591 patients admitted to intensive care units in Lombardy due to SARS-CoV-2 infection, 3% had a history of chronic liver disease. Patients with pre-existing cirrhosis might be more susceptible to SARS-CoV-2 infection because of their systemic immunocompromised status. Moreover, in these patients, the severity of COVID-19 and the rate of complications, potentially leading to increased liver-related mortality, might be more pronounced than in the general population.

Gastrointestinal Diseases

COVID-19 was originally considered a respiratory disease but increasing evidence identified the potentially serious systemic consequences involving major organs, including those of the digestive system.^[40] This review brings together the salient information relating to the digestive system, published up to September 2020. At the time of acceptance (October 2020), more than 43 million cases of COVID-19 have been reported worldwide with over 1 million deaths.^[41] SARS-CoV-2 is a single-stranded RNA virus, initially described as a serious acute respiratory virus of the coronavirus (SARS) family^[42] and is similar to those viruses which caused the 2002–2004 SARS epidemic, originating in China, and the 2012–2020 MERS outbreaks in the Middle East. COVID-19 is closely related to bat coronaviruses, suggesting COVID-19 has a similar zoonotic origin. The virus is highly contagious and spreads predominantly by respiratory droplets and aerosol while SARS-CoV-2 has been isolated from stool but fecal-oral spread has not been confirmed to date.

Risk Factors

Age

In the early phase of the outbreak, COVID-19 appeared to occur in older people in most world regions.^[43] A meta-analysis of 32 studies suggests that susceptibility in children/adolescents is half that of adults.^[44] However, other data indicate that young adults and children are as susceptible to the disease as older adults.^[45] In fact, significantly greater amounts of viral nucleic acid were detected in children (<5 yr; $n = 46$) than in adults (18–65 yr; $n = 48$).^[46] While the infection prevalence's relation to age is unclear, increased risk for severe illness evidently increases with age, making elders a high-risk population.^[47] The Centers for disease Control and Prevention reports that 8 of 10 COVID-19 deaths in the U.S. are over age 65.^[48] While, in-patient mortality rates in New York City were higher in those older than 65 versus those aged 18–65.^[47] Moreover, in-patient mortality rates in New York City were higher in those older than 65 versus those aged 18–65.^[47]

Sex

Despite similar sex distribution of individuals infected with SARS-CoV-2 (male 51%, female 49%), a sex difference is notable in COVID-19 fatality rates: males could be at higher risk than females for contracting severe COVID-19 (49). China's Center for disease Control and Prevention confirmed increased case fatality rates in males compared with females (2.8% vs. 1.7%, respectively), revealing that 64% of deaths in China have been male.^[50] Italy had similar trends: male mortality is apparently twice that of females in every age group. Italy's Public Health Research Agency noted that 59.8% of SARS-CoV-2 cases and 70% of national deaths so far have been male.^[51] New York City had increased hospitalized males more than females (60.3% vs. 39.7%, respectively; $n = 5,700$).^[47] Moreover, Open safely, an analytics platform covering over 17 million records in England, revealed that males have over one-half the mortality risk of females, HR: 1.59(1.53–1.65).^[52] Reduced SARS-CoV-2 infection in females could be attributed to their increased protection from viral infections by an additional X chromosome and varied sex hormones.^[53]

Race, Ethnicity, and Genetics

Current epidemiological data strongly indicate variability of case-fatality rates from as high as 15.1% in U.K., 14.2% in Italy, 3.3% in the U.S., and 2.1% in South Korea.^[54] Furthermore, increasing evidence suggests that COVID-19 disproportionately affects some racial and ethnic minority groups.^[55] The Open SAFELY extensive analytic platform indicated HR: 1.62–1.88 (adjusted for age and sex) for Black, South Asian, and mixed ethnicity, compared with white patients; and HR: 1.43–1.48 after adjustment of all included factors.^[52] Moreover, race/ethnicity data from the Morbidity and Mortality Weekly Report revealed that 33% of hospitalizations were for Blacks, two times the U.S. Black population. Conversely, 45% of those hospitalized

were white, less than half of the white population.^[56] Likewise, the Johns Hopkins University and American Community Survey reported that infection and death rates were more than three times and six times higher, respectively, in Black counties than in white ones in the U.S.^[57]

Researchers have also hypothesized possible genetic predisposition to ACE2 polymorphisms linked to diabetes, stroke, and hypertension.^[58] A meta-analysis ($n = 11,051$) provided strong evidence that ACE2 gene polymorphism G8790A had an increased risk factor for essential hypertension across different ethnic populations in female subjects and Han-Chinese male subjects.^[59] Genetic predispositions associated with increased comorbidities may factor into higher prevalence of heart disease, hypertension, diabetes, and obesity in minority groups, leading to increased COVID-19 susceptibility and severity. Although current but limited studies indicate possible genetic variability in COVID-19 contraction and/or severity, much is debated. Further research is needed to understand the molecular and pathophysiological mechanisms underlying the relationship among genetics, race/ethnic disparities, and COVID-19 infection and severity.

CONCLUSION

Corona patients are vulnerable to certain comorbidities, such as cardiovascular disease, hypertension, hepatic diseases, renal insufficiency, pulmonary diseases, neurological and hepatic disorders, in addition to risk factors, such as age, sex, race, ethnicity and Genetics. These comorbidities and risk factors often boost the risk of potentiating the already deteriorating condition of COVID-19. Thus, it essential to prevent and protect the condition of different comorbidities and take care of the risk factors in Covid-19 patients along with the treatment of Covid-19.

REFERENCES

1. LeBlanc JJ, Li Y, Bastien N, Forward KR, Davidson RJ, et al. Switching gears for an influenza pandemic: Validation of a duplex reverse transcriptase PCR assay for simultaneous detection and confirmatory identification of pandemic (H1N1)2009 influenza virus. *J Clin Microbiol*, 2009; 47: 3805-3813. doi:10.1128/JCM.01344-09. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Lu R, Zhao X, Li J, Niu P, Yang B, et al. 2020. Genomic characterization and epidemiology of novel coronavirus: implications for virus origins and receptor binding. *Lancet*, 2019; 395: 565-574. doi:10.1016/S0140-6736(20)30251-8. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. Richardson S, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*, 2020; 323: 2052-2059. Doi: 10.1001/jama.2020.6775. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Cheng Y, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.*, 2020; 97: 829-838. Doi:10.1016/j.kint.2020.03.005. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
5. Rodriguez-Morales AJ, et al. Clinical laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect. Dis.*, 2020; 34: 101623.
6. Drucker DJ. Coronavirus infections and type 2 diabetes—shared pathways with therapeutic implications. *Endocr. Rev.*, 2020; 41: 457-470. doi: 10.1210/endo/bnaa011. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Holman N, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol*, 2020; 8: 823-833. doi: 10.1016/S2213-8587(20)30271-0. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Grasselli G, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*, 2020; 323: 1574-1581. doi: 10.1001/jama.2020.5394. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
9. Yang J, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int. J. Infect. Dis.*, 2020; 94: 91-95. doi: 10.1016/j.ijid.2020.03.017. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Zhu L, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab*, 2020; 31: 1068-1077. doi: 10.1016/j.cmet.2020.04.021. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. *J Infect*, 2020; 81: e16-e25. doi:10.1016/j.jinf.2020.04.021. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. *J Renin-Angiotensin-Aldosterone Syst*, 2020; 21: 1470320320926899. doi:10.1177/1470320320926899. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. 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: 1054-1062. doi:10.1016/S0140-6736(20)30566-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

14. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.*, 2020; 8: e21. doi:10.1016/S2213-2600(20)30116-8. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Nehme A, Zouein FA, Zayeri ZD, Zibara K. An update on the tissue renin angiotensin system and its role in physiology and pathology. *J Cardiovasc Dev Dis.*, 2019; 6: 14. doi:10.3390/jcdd6020014. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Koka V, Xiao RH, Chung ACK, Wang W, Truong LD, Lan HY. Angiotensin II up-regulates angiotensin i-converting enzyme (ACE), but down-regulates ACE2 via the AT1-ERK/p38 MAP kinase pathway. *Am J Pathol.*, 2008; 172: 1174–1183. doi:10.2353/ajpath.2008.070762. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
17. Uri K, Fagyas M, Kertesz A, Borbely A, Jenei C, Bene O, et al. . Circulating ACE2 activity correlates with cardiovascular disease development. *J Renin-Angiotensin-Aldosterone Syst.*, 2016; 17: 1470320316668435. doi:10.1177/1470320316668435. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Li S, Wang Z, Yang X, Hu B, Huang Y, Fan S. Association between circulating angiotensin-converting enzyme 2 and cardiac remodeling in hypertensive patients. *Peptides*, 2017; 90: 63–68. doi:10.1016/j.peptides.2017.02.007. [PubMed] [CrossRef] [Google Scholar]
19. Ortiz-Pérez JT, Riera M, Bosch X, De Caralt TM, Perea RJ, Pascual J, Soler MJ. Role of circulating angiotensin converting enzyme 2 in left ventricular remodeling following myocardial infarction: a prospective controlled study. *PLoS One*, 2013; 8: e61695. doi:10.1371/journal.pone.0061695. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Silva-Aguiar RP, Peruchetti DB, Rocco PR, Schmaier AH, Silva PM, Martins MA, et al. Role of the renin-angiotensin system in the development of severe COVID-19 in hypertensive patients. *Am J Physiol Lung Cell Mol Physiol*, 2020; 319: L596–L602. doi:10.1152/ajplung.00286.2020. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
21. Guan WJ, Ni ZY, Hu Y, Liang WH, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of 2019 novel coronavirus infection in China. *N. Eng J Med.*, 2020; 382: 1708–1720. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Centers for Disease Control and Prevention (CDC). Scientific Evidence for Conditions that Increase Risk of Severe Illness | COVID-19 | CDC (Online). <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html> [24 July 2020].
23. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol*, 2020; 8: 813–822. doi:10.1016/S2213-8587(20)30272-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*, 2004; 203: 631–637. doi:10.1002/path.1570. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett.*, 2002; 532: 107–110. doi:10.1016/S0014-5793(02)03640-2. [PubMed] [CrossRef] [Google Scholar]
26. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-onset diabetes in Covid-19. *N Engl J Med.*, 2020; 383: 789–790. doi:10.1056/NEJMc2018688. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Codo AC, Davanzo GG, Monteiro L de B, de Souza GF, Muraro SP, Virgilio-da-Silva JV, et al. . Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1 α /glycolysis-dependent axis. *Cell Metab*, 2020; 32: 437–446. doi:10.1016/j.cmet.2020.07.007. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
28. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*, 2020; 369: 1966. doi:10.1136/bmj.m1966. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*, 2020; 395: 1763–1770. doi:10.1016/S0140-6736(20)31189-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
30. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*, 2020; 583(7816): 459–468. doi: 10.1038/s41586-020-2286-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.*, 2020; 383: 120–128. doi:10.1056/NEJMoA2015432. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol*, 2020; 33: 2128–2138. doi:10.1038/s41379-020-

- 0603-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. *J Pathol*, 2006; 210: 288–297. doi:10.1002/path.2067. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 34. Ramani A, Müller L, Ostermann PN, Gabriel E, Abida-Islam P, et al (2020) SARS-CoV-2 targets cortical neurons of 3D human brain organoids and shows neurodegeneration-like effects. *bioRxiv*. 10.1101/2020.05.20.106575
 35. Song E, Zhang C, Israelow B, Lu P, Weizman O-E, Liu F, et al (2020) Neuroinvasive potential of SARS-CoV-2 revealed in a human brain organoid model. *bioRxiv*. 10.1101/2020.06.25.169946
 36. Guan W.J., Ni Z.Y., Hu Y., Liang W.H., Ou C.Q., He J.X., China Medical Treatment Expert Group for Covid-19 Clinical characteristics of 2019 novel coronavirus infection in China. *N Engl J Med.*, 2020; 382: 1708–1720. [PMC free article] [PubMed] [Google Scholar]
 37. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, 2020; 395: 497–506. [PMC free article] [PubMed] [Google Scholar]
 38. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*, 2020; 395: 507–513. [PMC free article] [PubMed] [Google Scholar]
 39. Grasselli G., Zangrillo A., Zanella A., Antonelli M., Cabrini L., Castelli A., COVID-19 Lombardy ICU Network Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*, 2020; 323: 1574–1581. [PMC free article] [PubMed] [Google Scholar]
 40. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.*, Feb, 2020; 382(8): 727–33. [PMC free article] [PubMed] [Google Scholar]
 41. Johns Hopkins University COVID-19 daily dashboard [cited 2020 Oct 22] Available from: <https://coronavirus.jhu.edu/map.html>.
 42. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.*, Apr, 2020; 92(4): 418–23. [PMC free article] [PubMed] [Google Scholar]
 43. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, et al. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol*, 2020; 8: 782–792. doi:10.1016/S2213-8587(20)30238-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 44. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, et al. Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults. *JAMA Pediatrics*, 2021; 175: 143–156. doi:10.1001/jamapediatrics.2020.4573. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 45. Lopez AS, Hill M, Antezano J, Vilven D, Rutner T, et al. Transmission dynamics of COVID-19 outbreaks associated with child care facilities—Salt Lake City, Utah, April–July 2020. *MMWR Morb Mortal Wkly Rep.*, 2020; 69: 1319–1323. doi:10.15585/mmwr.mm6937e3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 46. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB et al. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). *JAMA Pediatr*, 2020; 174: 902. doi:10.1001/jamapediatrics.2020.3651. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 47. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, et al. The Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*, 2020; 323: 2052–2059. [Erratum in *JAMA* 323: 2098, 2020]. doi:10.1001/jama.2020.6775. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 48. Bialek S, Boundy E, Bowen V, Chow N, Cohn A, et al. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep.*, 2020; 69: 343–346. doi:10.15585/mmwr.mm6912e2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 49. Yang J, Zheng Y, Gou X, Pu K, Chen Z, 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: 91–95. doi:10.1016/j.ijid.2020.03.017. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
 50. Hua W, Xiaofeng L, Zhenqiang B, Jun R, Ban W, Liming L. Consideration on the strategies during epidemic stage changing from emergency response to continuous prevention and control. *Chinese J Endem*, 2020; 41: 297–300. doi:10.3760/cma.j.issn.0254-6450.2020.02.003. [PubMed] [CrossRef] [Google Scholar]
 51. Andrianou X, Bella A, Manso MD, Urdiales AM, Fabiani M, et al. force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità . *Epidemia COVID-19, Aggiornamento nazionale (Online)*. April 10, 2020; https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_9-aprile-2020.pdf. [Google Scholar]

52. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*, 2020; 584: 430–436. doi:10.1038/s41586-020-2521-4. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
53. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clin Rev Allergy Immunol*, 2019; 56: 308–321. doi:10.1007/s12016-017-8648-x. [PubMed] [CrossRef] [Google Scholar]
54. World Health Organization. Coronavirus Disease 2019 (110) (Online). <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. [2020].
55. Gold JA, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19—Georgia, March 2020. *MMWR Morb Mortal Wkly Rep.*, 2020; 69: 545–550. doi:10.15585/mmwr.mm6918e1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
56. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 states, March 1–30, 2020. *MMWR Morb Mortal Wkly Rep.*, 2020; 69: 458–464. doi:10.15585/mmwr.mm6915e3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
57. The Washington Post. African Americans are at Higher Risk of Death from Coronavirus (Online). <https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmpingly-high-rate-post-analysis-shows/?arc404=true> [30 Sep. 2020].
58. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.*, 2020; 8: e21. doi:10.1016/S2213-2600(20)30116-8. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
59. Lu N, Yang Y, Wang Y, Liu Y, Fu G, et al. ACE2 gene polymorphism and essential hypertension: an updated meta-analysis involving 11,051 subjects. *Mol Biol Rep.*, 2012; 39: 6581–6589. doi:10.1007/s11033-012-1487-1. [PubMed] [CrossRef] [Google Scholar]