

Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic impacting nearly 170 countries/regions and more than 285,000 patients worldwide. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which invades cells through the angiotensin converting enzyme 2 (ACE2) receptor. Among those with COVID-19, there is a higher prevalence of cardiovascular disease and more than 7% of patients suffer myocardial injury from the infection (22% of the critically ill). Despite ACE2 serving as the portal for infection, the role of ACE inhibitors or angiotensin receptor blockers requires further investigation. COVID-19 poses a challenge for heart transplantation, impacting donor selection, immunosuppression, and post-transplant management. Thankfully there are a number of promising therapies under active investigation to both treat and prevent COVID-19.

Key Words: COVID-19; myocardial injury; pandemic; heart transplant



Circulation

Coronavirus disease 2019 (COVID-19) is a global pandemic. As of March 21st, 2020 infected patients were present in 167 countries/regions around the world and there were more than 285,000 cases worldwide with nearly 12,000 fatalities.¹ While the outbreak began in China, the number of cases outside of China exceeded those in China on March 15th, 2020 and are currently rising at an exponential rate. Furthermore, the number of fatalities in Italy now exceeds the total in China. COVID-19 interacts with cardiovascular system on multiple levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction.

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This novel single-stranded enveloped RNA virus is the seventh known human coronavirus. SARS-CoV-2 is unlike the other coronaviruses known to cause the common cold (229E, OC43, NL63, and HKU1), but similar to the zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 (SARS)² and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012 (MERS).³ SARS-CoV-2 is believed to have originated in bats, similar to many other coronaviruses, as it shares 89-96% nucleotide identity with bat coronaviruses.⁴ Like SARS and MERS, it is believed SARS-CoV-2 moved from bats to an intermediate host (possibly a Malayan Pangolin, which shares 91% nucleotide identity) and then to humans.⁵ (Figure 1)

SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2).⁶ ACE2 is expressed in the lung (principally Type II alveolar cells⁷) and appears to be the predominant portal of entry. ACE2 is highly expressed in the heart as well, counteracting the effects of angiotensin II in states with

excessive activation of the renin-angiotensin system such as hypertension (HTN), congestive heart failure (CHF), and atherosclerosis.⁸ In addition to the heart and lung, ACE2 is expressed in the intestinal epithelium, vascular endothelium, and the kidneys, providing a mechanism for the multi-organ dysfunction that can be seen with SARS-CoV-2 infection.^{8,9} There is increasing evidence linking COVID-19 with increased morbidity and mortality from cardiovascular disease. In this review, we will summarize the rapidly evolving data in this field.

Clinical Presentation

SARS-CoV-2 is spread predominantly via respiratory droplets, but also can be aerosolized or detected in the stool. Transmission may occur from both symptomatic and asymptomatic patients, with secondary infection rates ranging 0.5-5%.^{10, 11} SARS-CoV-2 has been demonstrated to remain stable for up to 3 hours in the aerosolized form, up to 24 hours on cardboard, and as many as three days on plastic or stainless steel.¹² The median incubation time is 4-5 days and 97.5% will experience symptoms within 11.5 days of exposure.^{13, 14}

Early reports suggest the most common symptoms are fever (88%) and dry cough (67.7%), which are shared with many other viral syndromes (Figure 2). Conspicuously, rhinorrhea (4.8%) and gastrointestinal symptoms (diarrhea 4-14%, nausea/emesis 5%) appear to be less frequent with COVID-19.¹¹ Reports from China demonstrate that a significant majority of patients (81%) had mild symptoms (no pneumonia or mild pneumonia) from COVID-19. Among those with more significant symptoms, 14% experienced severe symptoms (dyspnea, respiratory rate ≥ 30 /min, blood oxygen saturation $\leq 93\%$, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , and/or lung infiltrates $> 50\%$ within 24 to 48 hours) and 5% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure).⁹

The case fatality rate (CFR, number of deaths/number of those diagnosed) has differed significantly around the world. The original reports from China suggested a CFR of 2.3%¹⁵ with subsequent reports estimating the symptomatic case fatality risk (the probability of dying after developing symptoms) was lower at 1.4%¹⁶, which contrasts with influenza (0.1%), MERS (34%), and SARS (10%).¹⁷ Based on reported data from March 21st, 2020, the CFR varies significantly by country: China 4.0% (81,304 cases), Italy 8.6% (47,021 cases), Iran 7.5% (20,610 cases), Spain 5.4% (25,374 cases), South Korea 1.2% (8,779 cases), Germany 0.3% (21,828 cases), and the United States 1.3% (22,043 cases).¹ The CFR rises rapidly with increasing age; the CFR is less than 1% for those under 50 years of age, rising to 1.3% for 50 year olds, 3.6% for 60 year olds, 8% for septuagenarians, and 14.8% for octogenarians.¹⁵ Similarly, the CFR increases with disease severity, as there were no deaths reported among the mild or severe cases in the Chinese cohort; however, the CFR was 49% among critical patients. Furthermore, compared to patients with no comorbidities in whom the CFR is 0.9%, patients with medical comorbidities have a significantly increased CFR: 10.5% for cardiovascular disease (CVD); 7.3% for diabetes mellitus (DM); 6.3% for COPD; 6% for HTN; and 5.6% for cancer.¹⁵

COVID-19 in Patients with Cardiovascular Disease

Cardiovascular disease was a common comorbidity in patients with COVID-19 predecessors SARS and MERS. In SARS, the prevalence of DM and CVD was 11% and 8% respectively, and the presence of either comorbidity increased the risk of death twelvefold.^{2, 18} DM and HTN were prevalent in about 50% of cases of MERS, while CVD was present in approximately 30% of patients.¹⁹ The increased presence of cardiovascular comorbidities holds true for COVID-19 as well, most notably among those with more severe disease. In one cohort of 191 patients from Wuhan, China, any comorbidity was present in 48% (67% of non-survivors), HTN was present

in 30% (48% of non-survivors), DM in 19% (31% of non-survivors), and CVD in 8% (13% of non-survivors).²⁰ In a cohort of 138 hospitalized patients with COVID-19, comorbidities were similarly prevalent (46% overall, 72% in patients requiring an ICU), as were cardiovascular comorbidities: HTN in 31% (58% in patients requiring an ICU), CVD in 15% (25% in patients requiring an ICU), and DM in 10% (22% in patients requiring an ICU).²¹ Analysis of an outpatient and inpatient cohort of 1,099 patients with COVID-19 reported that 24% had any comorbidity (58% among those with intubation or death), with 15% having HTN (36% among those with intubation or death), 7.4% with DM (27% among those with intubation or death), and 2.5% with coronary heart disease (9% among those with intubation or death).¹³ Data from the National Health Commission (NHC) of China demonstrated that 35% of patients diagnosed with COVID-19 had HTN and 17% had coronary heart disease.²² Lastly, a recent meta-analysis of eight studies from China including 46,248 infected patients showed the most prevalent comorbidities were HTN (17±7%, 95% CI 14-22%) and DM (8±6%, 95% CI 6-11%), followed by cardiovascular diseases (5±4%, 95% CI 4-7%).²³ The mechanism of these associations remains unclear at this time. Potential explanations include CVD being more prevalent in those with advancing age, a functionally impaired immune system, elevated levels of ACE2, or a predisposition to COVID-19 for those with CVD.

COVID-19 and Myocardial Injury

Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases in China. In the aforementioned study of 138 hospitalized patients with COVID-19 in Wuhan China, cardiac injury (elevated high sensitivity Troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities) was present in 7.2% of patients overall, and 22% that required ICU care.²¹ The report from the NHC of China reported that almost 12% of patients without

known CVD had elevated troponin levels or cardiac arrest during the hospitalization.²² Notably, hs-cTnI was above the 99th percentile upper reference limit in 46% of non-survivors as opposed to 1% of survivors.²⁰ (Figure 3)

Early reports indicate that there are two patterns of myocardial injury with COVID-19. One study demonstrated that at 4 days following symptom onset, median hs-cTnI levels were 8.8 pg/mL in non-survivors vs. 2.5 pg/mL in survivors. During follow-up, the median hs-cTnI among survivors did not change significantly (2.5-4.4 pg/mL), whereas it rose to 24.7 pg/mL on Day 7, to 55.7 pg/mL on Day 13, to 134.5 pg/mL on Day 19, and to 290.6 pg/mL on Day 22 for non-survivors.²⁰ Notably, the median time to death from the onset of symptoms was 18.5 days (IQR 15 – 20 days). The rise in hs-cTnI tracks with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase), raising the possibility that this reflects cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury. In contrast, reports of patients presenting with predominantly cardiac symptoms suggest a different pattern, potentially viral myocarditis or stress cardiomyopathy. For example, one case recently published involved a man presenting with chest pain and ST-segment elevation on his electrocardiogram, but without coronary obstruction. An echocardiogram noted left ventricular dysfunction (ejection fraction 27%, LVEDD 5.8cm) and elevated cardiac biomarkers (troponin T >10 ng/mL, NT-proBNP>21,000 pg/mL).²⁴ Following a therapeutic approach which included intravenous immunoglobulin and steroids, ejection fraction and cardiac biomarkers normalized within three weeks. In another report from China, a 63 year old man with no past cardiac history presented with both severe respiratory manifestation and evidence of fulminant myocarditis with an enlarged left ventricle (LVEDD 6.1 cm) and depressed left ventricular function (ejection fraction 32%). The patient had an elevated troponin-I (>11 ng/mL) and NT-proBNP (>22,000

pg/ml). Given the severity of his cardiogenic shock, he was placed on extracorporeal membrane oxygenation and was treated with intravenous immunoglobulin, steroids, anti-viral therapy and renal replacement therapy. The patient ultimately showed recovery of his ventricular function within 2 weeks.²⁵ While both of these patients were treated with glucocorticoids it is unclear the impact of this therapy, as both the WHO and CDC currently do not recommend glucocorticoid use unless otherwise indicated (e.g. chronic obstructive pulmonary disease or asthma exacerbation).^{26, 27} Similarly a report from the NHC of China comments that a subset of patients presented with palpitations and chest pain, not the typical fever and cough.²² Based on available but limited data, it appears that the incidence of fulminant myocarditis and profound cardiogenic shock is low; however, the rate of recovery and mode of treatment are yet to be determined.

The exact mechanism of cardiac involvement in COVID-19 remains under investigation. One potential mechanism is direct myocardial involvement mediated via ACE2. A murine model demonstrated pulmonary infection with SARS-CoV also precipitated an ACE2-dependent myocardial infection.²⁸ Among humans, during the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of autopsied hearts.²⁹ Other suggested mechanisms of COVID-19 related cardiac involvement include a cytokine storm, mediated by an imbalanced response among subtypes of T helper cells²⁰, and hypoxia induced excessive intracellular calcium leading to cardiac myocyte apoptosis.²²

Role of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB)

ACE2 is a homolog of ACE that converts angiotensin II to angiotensin 1-7, thereby diminishing vasoconstriction mediated by the renin angiotensin system. The use of ACEi and ARB are common in cardiovascular disorders (HTN, coronary artery disease, congestive heart failure, and

DM). There are conflicting data from studies demonstrating whether these drugs increase³⁰⁻³² or have minimal effect on ACE2 levels³³⁻³⁶. SARS-CoV-2 entry into cells is ACE2 dependent (Figure 4); however, ACE2 appears to be protective against acute lung injury. In a murine model, binding of the SARS-CoV spike protein to ACE2 caused ACE2 downregulation, leading to an increase in angiotensin II and ultimately increased pulmonary vascular permeability, inducing pulmonary edema, and reduced lung function. However, treatment with recombinant ACE2³⁷ and losartan³⁸ mitigated the degree of lung injury. On this basis losartan is being studied for potential mitigation of lung injury among both inpatients and outpatients with COVID-19.^{39, 40} At this time nearly all major societies have recommended against adding or stopping ACEi, ARB, or other RAAS antagonists in this setting, unless done on clinical grounds independently of COVID-19, given the lack of evidence currently available on their potential benefit or harm.



Heart Transplantation in the Era of COVID-19

During prior coronavirus epidemics (SARS & MERS), transplant patients presented with similar symptoms as the general population.^{41, 42} In the current pandemic, a case study described the clinical courses of two heart transplant recipients from the Hubei province of China. Both patients presented with fevers and had laboratory and CT scans that were similar to non-immunosuppressed individuals with bilateral ground glass opacities in a peripheral distribution. One had relatively mild disease, while the other required hospitalization requiring supplemental oxygen.⁴³ Both survived and were treated with antibiotics and antivirals, while the more ill patient also required cessation of immunosuppression, along with treatment with methylprednisolone and IVIG. A survey of 87 heart transplant recipients in Wuhan, China did not find a higher risk of infection with SARS-CoV-2 if routine preventive measures were used, and while encouraging, this needs to be confirmed in larger populations.⁴⁴ Further, we do not

know if transplant patients will experience differences in disease severity or duration compared with the non-immunosuppressed population.

The ongoing pandemic has raised the question of whether to continue offering heart transplantation due to concerns about a risk for exposure to COVID-19 during hospitalization, as well as challenges in controlling the infection in the context of high levels of immunosuppression. Current recommendations are to continue heart transplantation without changes in immunosuppression provided the recipient has not tested positive for SARS-CoV-2 and has not had exposure to or symptoms of COVID-19 in the prior two to four weeks.^{45, 46} Major societal recommendations include avoiding donors with known or suspected COVID-19 and if a donor had COVID-19, they should be COVID-19 free (by PCR) for at least 14 days (owing to the incubation period of ~5 days and onset of symptoms in ~11.5 days).^{14, 47} We recognize the difficulties of this decision with increasing prevalence of COVID-19 in the donor population, that may be asymptomatic, especially if the donor cannot be tested for COVID-19. Recommended management of transplant recipients who developed COVID-19, based on very limited data to date, is supportive care and continuation of immunosuppression for mild COVID-19 with reduction of the anti-metabolite (mycophenolate or azathioprine) and further treatment based on disease severity and drug availability.⁴⁵ Notably, one potential treatment option for COVID-19 are protease inhibitors, which will increase calcineurin inhibitor levels.

Treatment

Preventive measures are the best strategy for COVID-19 at this time. While vaccines and monoclonal antibodies against SARS-CoV-2 are in development, a number of other investigational therapies, using repurposed clinically approved drugs targeting SARS-CoV-2 cell invasion and replication, may be considered. Recombinant human ACE2 (APN01) was

developed in 2010 and could potentially both neutralize the virus and protect against acute lung injury. It has been demonstrated to be safe and reduce levels of both angiotensin II and IL-6 in a Phase II study of acute respiratory distress syndrome⁴⁸. It is currently under investigation in China in severe COVID-19. The serine protease inhibitor camostat mesylate, which is approved in Japan for chronic pancreatitis and postoperative reflux esophagitis among other indications, has been shown to block TMPRSS2 activity and inhibit SARS-CoV entry into cells.⁴⁹ This well tolerated therapy has been proposed as a treatment to prevent SARS-CoV-2 spike protein activation, thereby preventing cell entry and controlling infection. Remdesevir is a broad spectrum antiviral that interrupts RNA replication by acting as a nucleotide analog.⁵⁰ Initially developed to treat Ebola, it has been demonstrated to have both *in vitro* activity against SARS-CoV-2 and prevent and reduce disease severity in MERS-CoV in primates.^{51, 52} It has been safe in prior trials and currently is enrolling in clinical trials in China^{53, 54} and the United States.^{55, 56} Chloroquine (anti-malarial drug) and hydroxychloroquine (rheumatoid arthritis or systemic lupus erythematosus treatment) block SARS-CoV-2 cell entry *in vitro* at similar concentrations that are achieved with treatment for rheumatoid arthritis (500 mg twice daily for chloroquine & 600 mg twice a day loading followed by 400-600 mg a day for hydroxychloroquine) and trials with these agents are ongoing.^{52, 57-60} Additionally, early studies suggest clinical benefit in COVID-19 with reduction in pneumonia severity, decreased length of hospitalization, and earlier viral clearance.⁶¹ The combination protease inhibitor lopinavir/ritonavir used in HIV was demonstrated to have *in vitro* activity against SARS-CoV and improved clinical outcomes when used in combination with ribavirin for SARS.⁶² There have been reports of its success in treating SARS-CoV-2, though the first randomized control trial did not demonstrate statistically significant benefit among hospitalized patients with COVID-19.⁶³ In this study of 199 patients,

28 day mortality was 5.8% lower (95% CI -17.3-5.7%) for the lopinavir/ritonavir treated patients and the median time to improvement was 1 day shorter; further data are needed to determine the role of lopinavir/ritonavir. Antiviral medications typically used for influenza (oseltamivir and arbidol) have been applied, without clinical efficacy data available. Another drug approved for influenza, favipiravir, is considered promising as it inhibits RNA polymerase and is being studied in a clinical trial in China.⁶⁴ Other proposed strategies include interferon and convalescent serum.

Tocilizumab and sarilumab are IL-6 receptor antagonists used in the treatment of rheumatoid arthritis, while tocilizumab also has the indication for the treatment of cytokine release syndrome as is seen with chimeric antigen receptor-T cell (CAR-T) therapy. These may be potential therapies for COVID-19 patients that display elements of cytokine storm or secondary hemophagocytic lymphohistiocytosis with markedly elevated IL-6, ferritin, D-dimer, and hs-cTnI levels. Tocilizumab has been used with reported success for patients with severe COVID-19 and there are ongoing clinical trials⁶⁵⁻⁶⁷ and a trial of sarilumab just launched in the United States.⁶⁸

Conclusion

COVID-19, caused by SARS-CoV-2, is a global pandemic evolving in real time. Cardiovascular comorbidities are common in patients with COVID-19 and such patients are at higher risk of morbidity and mortality. However, it is not known if the presence of cardiovascular comorbid conditions pose independent risk or whether this is mediated by other factors (e.g. age).

Myocardial injury is present in more than a quarter of critical cases and presents in two patterns: acute myocardial injury and dysfunction on presentation and myocardial injury that develops as illness severity intensifies. The continuation of clinically indicated ACEi and ARB medications

is recommended based on the available evidence at this time. There are a number of promising treatments under investigation, but none with proven clinical efficacy to date.

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References

1. Dong E, Du H and Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. Feb 19, 2020. doi: 10.1016/S1473-3099(20)30120-1. [epub ahead of print] Accessed 3/21/20.
2. Chan JWM, Ng CK, Chan YH, Mok TYW, Lee S, Chu SY, Law WL, Lee MP and Li PCK. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). *Thorax*. 2003;58:686-689.
3. Badawi A and 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;49:129-133.
4. Andersen KG, Rambaut A, Lipkin WI, Holmes EC and Garry RF. The proximal origin of SARS-CoV-2. *Nat Med*. March 17, 2020. doi: 10.1038/s41591-020-0820-9. [epub ahead of print].
5. Zhang T WQ, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Curr Biol*. March 13, 2020. doi: 10.1016/j.cub.2020.03.022. [epub ahead of print]
6. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C and Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. March 5, 2020. doi: 10.1016/j.cell.2020.02.052. [epub ahead of print].

7. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y and Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv. January 26, 2020. doi: 10.1101/2020.01.26.919985.
8. Tikellis C and Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *Int J Pept*. 2012;2012:256294-256294.
9. Zhang H, Penninger JM, Li Y, Zhong N and Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*. March 3, 2020. doi: 10.1007/s00134-020-05985-9. [epub ahead of print].
10. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M and Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *New Eng J Med*. 2020;382:1177-1179.
11. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). February 28, 2020. [https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-\(covid-19\)](https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)).
12. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E and Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *New Eng J Med*. March 17, 2020. doi: 10.1056/NEJMc2004973. [epub ahead of print].
13. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, Liu L, Shan H, Lei C-l, Hui DSC, Du B, Li L-j, Zeng G, Yuen K-Y, Chen R-c, Tang C-l, Wang T, Chen P-y, Xiang J, Li S-y, Wang J-l, Liang Z-j, Peng Y-x, Wei L, Liu Y, Hu Y-h, Peng P, Wang J-m, Liu J-y, Chen Z, Li G, Zheng Z-j, Qiu S-q, Luo J, Ye C-j, Zhu S-y and Zhong N-s. Clinical Characteristics of Coronavirus Disease 2019 in China. *New Eng J Med*. February 28, 2020. doi: 10.1056/NEJMoa2002032. [epub ahead of print].
14. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG and Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med*. March 10, 2020. doi: 10.7326/M20-0504. [epub ahead of print].
15. Wu Z and 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*. Feb 24, 2020. doi: 10.1001/jama.2020.2648. [epub ahead of print].
16. Wu JT, Leung K, Bushman M, Kishore N, Niehus R, de Salazar PM, Cowling BJ, Lipsitch M and Leung GM. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat Med*. March 19, 2020. doi: 10.1038/s41591-020-0822-7. [epub ahead of print].
17. Munster VJ, Koopmans M, van Doremalen N, van Riel D and de Wit E. A Novel Coronavirus Emerging in China — Key Questions for Impact Assessment. *New Eng J Med*. 2020;382:692-694.
18. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephtimios IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM and Detsky AS. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *Jama*. 2003;289:2801-2809.

19. Badawi A and 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;49:129-133.
20. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H and Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet.* March 11, 2020. doi: 10.1016/S0140-6736(20)30566-3. [epub ahead of print].
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X and Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* 2020;323:1061-1069.
22. Zheng Y-Y, Ma Y-T, Zhang J-Y and Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* March 5, 2020. doi: 10.1038/s41569-020-0360-5. [epub ahead of print].
23. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y and Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis.* March 12, 2020. doi: 10.1016/j.ijid.2020.03.017. [epub ahead of print].
24. Hu H, Ma F, Wei X and Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J.* March 16, 2020. doi: 10.1093/eurheartj/ehaa190. [epub ahead of print].
25. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, Wang LF, Gao H, Wang Y, Dong CF, Li YJ, Xie XJ, Feng C and Liu L. First Case of COVID-19 Infection with Fulminant Myocarditis Complication: Case Report and Insights. *preprints.* 2020; 2020030180. doi: 10.20944/preprints202003.0180.v1.
26. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Revised March 7th, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>.
27. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. March 13, 2020. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
28. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM and Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest.* 2009;39:618-625.
29. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephtimios IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM and Detsky AS. Clinical Features and Short-term Outcomes of 144 Patients With SARS in the Greater Toronto Area. *JAMA.* 2003;289:2801-2809.
30. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB and Ferrario CM. Upregulation of Angiotensin-Converting Enzyme 2 After Myocardial Infarction by Blockade of Angiotensin II Receptors. 2004;43:970-976.
31. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI and Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation.* 2005;111:2605-2610.

32. Ocaranza MP, Palomera C, Román M, Bargetto J, Lavandero S and Jalil JE. Effect of hypertension on angiotensin-(1-7) levels in rats with different angiotensin-I converting enzyme polymorphism. *Life sciences*. 2006;78:1535-1542.
33. Klimas J, Olvedy M, Ochodnicka-Mackovicova K, Kruzliak P, Cacanyiova S, Kristek F, Krenek P and Ochodnický P. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. *J Cell Mol Med*. 2015;19:1965-1974.
34. Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E and Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. *EP Europace*. 2016;19:1280-1287.
35. Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK and Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in experimental myocardial infarction: implications for future therapeutic directions. *Clinical Science*. 2012;123:649-658.
36. Burrell LM, Risvanis J, Kubota E, Dean RG, MacDonald PS, Lu S, Tikellis C, Grant SL, Lew RA, Smith AI, Cooper ME and Johnston CI. Myocardial infarction increases ACE2 expression in rat and humans. *Eur Heart J*. 2005;26:369-75; discussion 322-324.
37. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui C-C, Hein L, Uhlig S, Slutsky AS, Jiang C and Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436:112-116.
38. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C and Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875-879.
39. ClinicalTrials.gov. Randomized Controlled Trial of Losartan for Patients With COVID-19 Not Requiring Hospitalization. Identifier: NCT04311177. March 17, 2020. <https://clinicaltrials.gov/ct2/show/NCT04311177>.
40. ClinicalTrials.gov. Randomized Controlled Trial of Losartan for Patients With COVID-19 Requiring Hospitalization. Identifier: NCT04312009. March 17, 2020. <https://clinicaltrials.gov/ct2/show/NCT04312009>.
41. AlGhamdi M, Mushtaq F, Awn N and Shalhoub S. MERS CoV Infection in Two Renal Transplant Recipients: Case Report. *Am J Transplant*. 2015;15:1101-1104.
42. Kumar D, Tellier R, Draker R, Levy G and Humar A. Severe Acute Respiratory Syndrome (SARS) in a Liver Transplant Recipient and Guidelines for Donor SARS Screening. *Am J Transplant*. 2003;3:977-981.
43. Li F, Cai J and Dong N. First Cases of COVID-19 in Heart Transplantation From China. *J Heart Lung Transplant*. 2020. doi: 10.1016/j.healun.2020.03.006. [epub ahead of print].
44. Zong-Li Ren RH, Zhi-Wei Wang, Min Zhang, Yong-Le Ruan , Zhi-Yong Wu , Hong-Bing Wu , Xiao-Ping Hu, Zhi-Peng Hu, Wei Ren, Luo-Cheng Li, Fei-Feng Dai, Huan Liu, Xin Cai. Epidemiological and Clinical Characteristics of Heart Transplant Recipients During the 2019 Coronavirus Outbreak in Wuhan, China: A Descriptive Survey Report. *J Heart Lung Transplant*. 2020. doi: 10.1016/j.healun.2020.03.008. [epub ahead of print].
45. Guidance for Cardiothoracic Transplant and Mechanical Circulatory Support Centers regarding SARS CoV-2 infection and COVID-19: March 17, 2020.

<https://community.ishlt.org/HigherLogic/System/DownloadDocumentFile.ashx?DocumentFileKey=afb06f06-5d63-13d4-c107-d152a9f6cd46>.

46. American Society of Transplantation. 2019-nCoV (Coronavirus): FAQs for Organ Transplantation. Updated Feb 29, 2020. <https://www.myast.org/sites/default/files/COVID19%20FAQ%20Tx%20Centers%20030220-1.pdf>.
47. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM and Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *New Eng J Med*. January 29, 2020. doi: 10.1056/NEJMoa2001316. [epub ahead of print].
48. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI and Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Critical Care*. 2017;21:234.
49. Kawase M, Shirato K, van der Hoek L, Taguchi F and Matsuyama S. Simultaneous Treatment of Human Bronchial Epithelial Cells with Serine and Cysteine Protease Inhibitors Prevents Severe Acute Respiratory Syndrome Coronavirus Entry. *J Virol*. 2012;86:6537-6545.
50. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP and Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem*. Feb 24, 2020. doi: 10.1074/jbc.AC120.013056 [epub ahead of print].
51. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, Scott D, Cihlar T and Feldmann H. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *PNAS*. Feb 13, 2020;201922083. doi: 10.1073/pnas.1922083117. [epub ahead of print].
52. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W and Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269-271.
53. ClinicalTrials.gov. Severe 2019-nCoV Remdesivir RCT. Identifier: NCT04257656. Last Updated Feb 24, 2020. <https://clinicaltrials.gov/ct2/show/NCT04257656>.
54. ClinicalTrials.gov. Mild/Moderate 2019-nCoV Remdesivir RCT. Identifier: NCT04252664. Last Updated Feb 24, 2020. <https://clinicaltrials.gov/ct2/show/NCT04252664>.
55. ClinicalTrials.gov. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19). Identifier: NCT04292899. Updated March 19, 2020. <https://clinicaltrials.gov/ct2/show/NCT04292899>.
56. ClinicalTrials.gov. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. Identifier: NCT04292730. Updated March 19, 2020. <https://clinicaltrials.gov/ct2/show/NCT04292730>.
57. ClinicalTrials.gov. Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19). Identifier: NCT04307693. Updated March 13, 2020. <https://clinicaltrials.gov/ct2/show/NCT04307693>.

58. ClinicalTrials.gov. Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV). Identifier: NCT04261517. Updated March 4, 2020. <https://clinicaltrials.gov/ct2/show/NCT04261517>.
59. ClinicalTrials.gov. Post-exposure Prophylaxis for SARS-Coronavirus-2. Identifier: NCT04308668. Updated March 19, 2020. <https://clinicaltrials.gov/ct2/show/NCT04308668>.
60. ClinicalTrials.gov. Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting (COPCOV). Identifier: NCT04303507. Updated March 11, 2020. <https://clinicaltrials.gov/ct2/show/NCT04303507>
61. Gao J, Tian Z and Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BioSci Trends*. 2020;14:72-73.
62. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS and Yuen KY. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59:252-256.
63. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D and Wang C. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *New Eng J Med*. March 18, 2020. doi: 10.1056/NEJMoa2001282. [epub ahead of print].
64. Furuta Y, Komeno T and Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc Jpn Acad Ser B Phys biol sci*. 2017;93:449-463.
65. ClinicalTrials.gov. Tocilizumab in COVID-19 Pneumonia (TOCIVID-19) (TOCIVID-19). Identifier: NCT04317092. Updated March 20, 2020. <https://www.clinicaltrials.gov/ct2/show/NCT04317092>.
66. ClinicalTrials.gov. Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS). Identifier: NCT04306705. Updated March 17, 2020. <https://clinicaltrials.gov/ct2/show/NCT04306705>.
67. ClinicalTrials.gov. Tocilizumab for SARS-CoV2 Severe Pneumonitis. Identifier: NCT04315480. Updated March 19, 2020. <https://clinicaltrials.gov/ct2/show/NCT04315480>.
68. ClinicalTrials.gov. Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. Identifier: NCT04315298. Updated March 19, 2020. <https://www.clinicaltrials.gov/ct2/show/NCT04315298>.

Figure Legends

Figure 1. Suspected transmission pathway of SARS-CoV-2 to humans

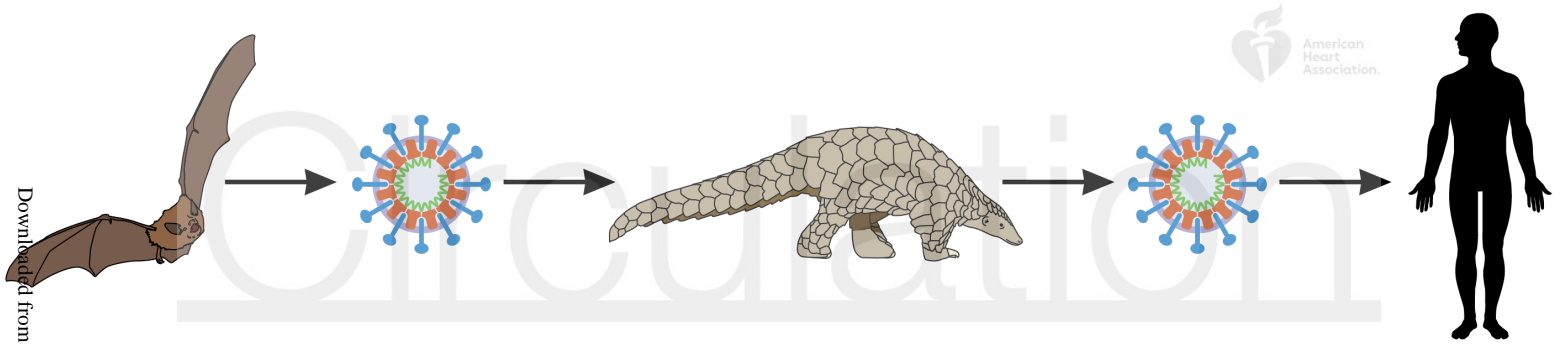
Figure 2. Symptoms of COVID-19

Figure 3. Myocardial injury during COVID-19 can be explained by two mechanisms. 1) From the associated cytokine storm manifested by elevated levels of IL-6, ferritin, LDH, and D-dimer. 2) Myocardial dysfunction from the direct effect of SARS-CoV-2 on the heart.

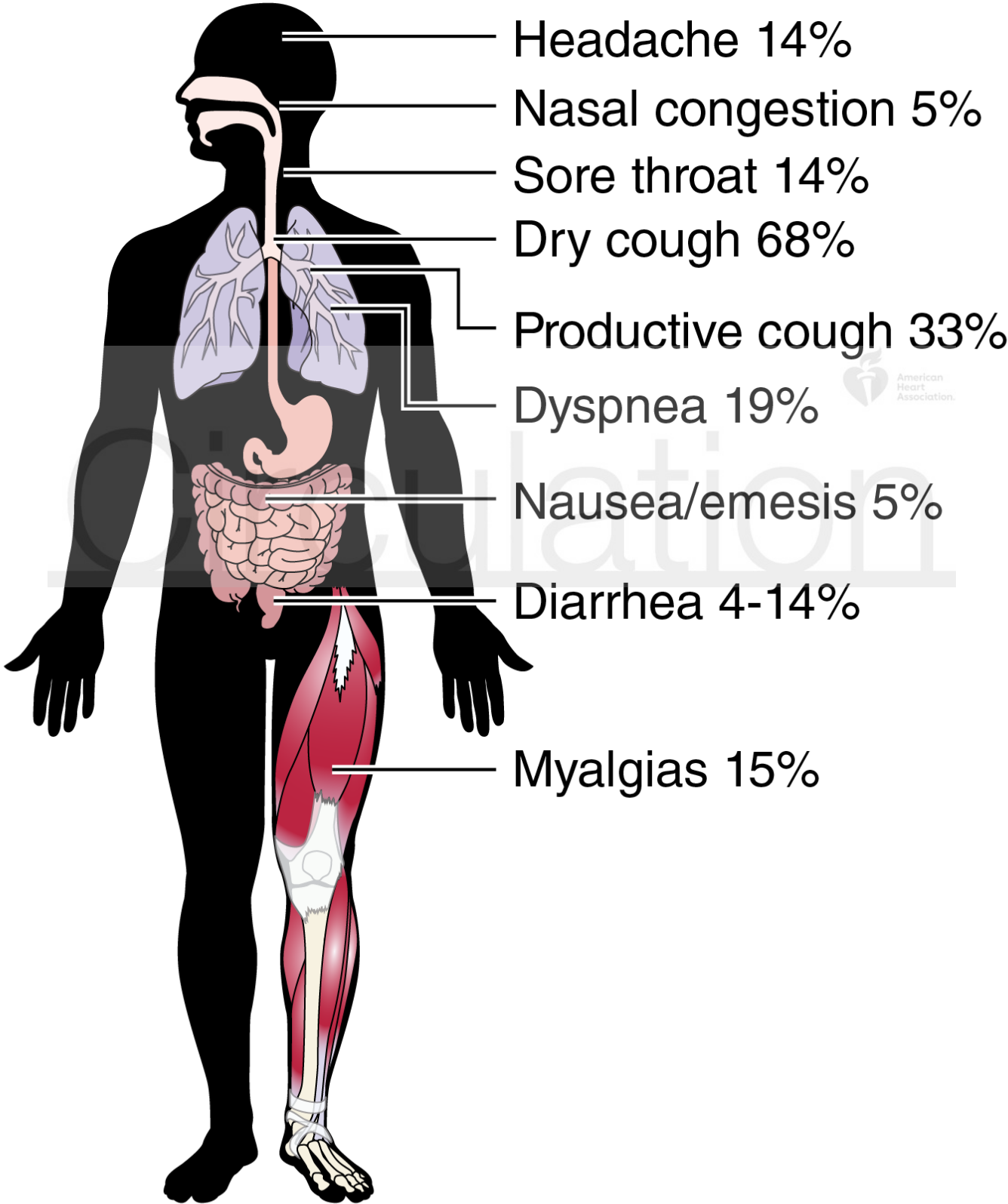
Figure 4. SARS-CoV-2 binds to the ACE2 receptor following activation of the spike protein by TMPRSS2

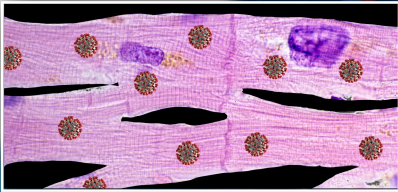


Circulation



Fever	88%
Fatigue	38%
Chills	11%



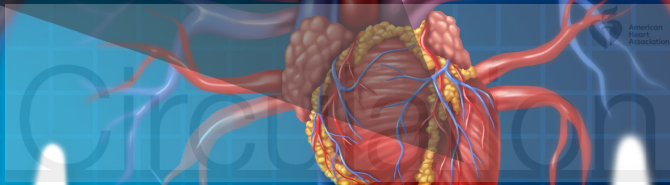


IL6 ↑↑

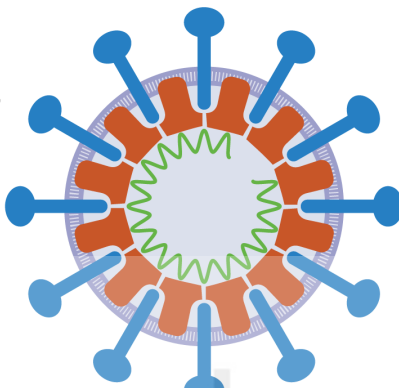
D-Dimer ↑↑

Ferritin ↑↑

LDH ↑↑



SARS-CoV
SARS from 2002-2003
&
SARS-Cov-2
COVID-19



Attachment protein "spike"



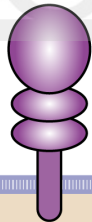
The spike protein of SARS-CoV-2 is primed by TMPRSS2

Activation

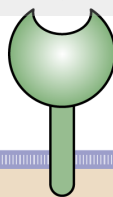
Attachment

SARS-Cov-2 uses the ACE2 receptor for host cell entry

TMPRSS2



Angiotensin converting enzyme (ACE2)



Host cell