

Crosstalk between coronavirus disease 2019 and cardiovascular disease and its treatment

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Abstract

People with cardiovascular disease (CVD) often contract coronavirus disease 2019 (COVID-19). However, the interaction between COVID-19 and CVD is unclear. In this systematic review, the available evidence for the crosstalk between COVID-19 and CVD and its treatment was analysed. A search was performed in the electronic databases MEDLINE and EMBASE. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects human cells via angiotensin-converting enzyme 2. SARS-CoV-2 can cause CVD by inducing cytokine storms, creating an imbalance in the oxygen supply and demand and disrupting the renin–angiotensin–aldosterone system; SARS-CoV-2 infection can also lead to the development of CVD through the side effects of therapeutic drugs, psychological factors, and aggravation of underlying CVD. The most common CVDs caused by SARS-CoV-2 infection are acute myocardial injury, arrhythmia, and heart failure. Studies have found that there is an interaction between COVID-19 and CVD. Underlying CVD is associated with a high risk of mortality in patients with COVID-19. SARS-CoV-2 infection can also cause new-onset CVD. Clinicians need to pay close attention to cardiovascular complications during the diagnosis and treatment of patients with COVID-19 to reduce patient mortality.

Keywords COVID-19; SARS-CoV-2; Cardiovascular disease; Renin–angiotensin–aldosterone system

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in China in late December 2019 and broke out in Wuhan. There are now > 1 000 000 confirmed cases worldwide. Because it is highly contagious, the population is generally susceptible, it has a long incubation period, and its diverse clinical manifestations and other characteristics pose a serious threat to human health. Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) belongs to the β -coronaviruses. It is a single-stranded positive-sense RNA virus with a nonsegmented envelope and a diameter of 50 to 200 nm.¹ It is currently the seventh member of the genus *Coronavirus* that can infect humans. Of the other six coronaviruses that have been identified as infecting humans, four (229E, OC43, NL63, and HPU1) are widespread but only cause common upper respiratory infection

symptoms. The other two are SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), which can cause fatal diseases.² Whole-genome sequencing results showed that the SARS-CoV-2 genome has 79.5% sequence identity with the SARS-CoV genome, and the virus is considered to be associated with SARS-CoV.³ SARS-CoV-2 infection mainly affects the respiratory tract, and the first clinical manifestations are mostly fever, dry cough, fatigue, and wheezing. Severe cases can progress to severe pneumonia, acute respiratory distress syndrome, and systemic multiple organ dysfunction.⁴ However, it is worth noting that increasing case data show that SARS-CoV-2 infection can cause cardiovascular events,^{5,6} which aggravate the condition and affect the prognosis; these cardiovascular events include acute myocardial injury and arrhythmia and cardiac dysfunction, in addition to causing respiratory diseases.^{4,7}

This article summarizes the treatment experience of frontline clinical experts and refers to the published literature and the new coronavirus pneumonia diagnosis and treatment programme (trial version 7) issued by the Chinese Health Commission to discuss the mechanism and treatment of cardiovascular disease (CVD) caused by COVID-19. We hope this information can be helpful to our counterparts at home and abroad.

Interaction between coronavirus disease 2019 and cardiovascular disease

CVD is the most common noncommunicable epidemic in China⁸ and around the world.⁹ CVD is present in nearly 20% of the total population, and the number of cardiovascular patients is as high as 290 million in China.¹⁰ Therefore, many COVID-19 patients have coexisting chronic CVD. As of 11 February 2020, out of the 44 672 patients confirmed to have COVID-19, 2683 patients (12.8%) had hypertension and 873 patients (4.2%) had CVD.¹¹ This is the most common co-morbid condition among patients admitted to the hospital for COVID-19.^{4,7} The mortality rate of COVID-19 patients with CVD was found to be 10.5%, the mortality rate of COVID-19 patients with hypertension was 6.0%, and the mortality rate of COVID-19 patients without co-morbidities was 0.9%.¹² The Chinese Center for Disease Control and Prevention's analysis of 72 314 cases of COVID-19 in China found that the current crude mortality rate of COVID-19 is 2.6%, while the mortality rate is 10.5% in patients with CVD.¹³ Death occurs in COVID-19 patients with CVD approximately 11 times more frequently than in patients without co-morbid CVD.¹¹ In another study, a retrospective analysis of 112 COVID-19 patients with CVD admitted to Wuhan Xiehe Hospital from 20 January 2020 to 15 February 2020 reported that there were 17 deaths, with a mortality rate of 15.2%.¹⁴ Hospitalized patients in Northern Italy with concomitant cardiac disease and COVID-19 had an extremely poor prognosis than had subjects without a history of cardiac disease, with a higher mortality rate.¹⁵ Experimental research also found that patients with basic heart diseases exhibited increased expression of angiotensin-converting enzyme 2 (ACE2) and a high probability of heart attack and progression to severe disease after SARS-CoV-2 infection.¹⁶ The assessment of ACE2 expression in normal and diseased human myocardial samples by bulk nuclei and single-nucleus RNA-seq suggests that prior CVD is the predominant driver of cardiomyocyte-specific increased transcription of ACE2.¹⁷ These findings may provide a pathological link between SARS-CoV-2 infection and viral myocarditis, helping explain why individuals with underlying CVD have a worse prognosis and higher mortality after infection with SARS-CoV-2.^{18,19}

A retrospective single-centre case series analysed patients with COVID-19 at the Seventh Hospital of Wuhan City, China, from 23 January 2020 to 23 February 2020.²⁰ They found that the mortality rate during hospitalization was 7.6% (8 of 105) in COVID-19 patients without underlying CVD and with normal troponin protein T (TnT) levels, 13.3% (4 of 30) in those with underlying CVD and normal TnT levels, 37.5% (6 of 16) in those without underlying CVD but with elevated TnT levels, and 69.4% (25 of 36) in those with underlying CVD and elevated TnT levels. Patients with underlying CVD were more likely to have elevated TnT levels than patients without CVD (36 [54.5%] vs. 16 [13.2%]).²⁰ In another cohort study of 416 patients with confirmed cases of COVID-19 who were consecutively enrolled in a centre of the People's Hospital of Wuhan University, China, from 20 January 2020 to 10 February 2020, cardiac injury during hospitalization occurred in 19.7% of the patients, and cardiac injury was found to be an independent risk factor for in-hospital death.²¹ A study population including 99 consecutive patients with COVID-19 admitted to the hospital between 4 and 25 March 2020 in Italy found that mortality was higher in 53 COVID-19 patients with cardiac disease than in 46 COVID-19 patients without cardiac disease (36% vs. 15%, log-rank $P = 0.019$; relative risk 2.35; 95% confidence interval 1.08–5.09).¹⁵ These results indicate not only that underlying CVD is a high-risk factor for death in people with COVID-19 but also that secondary myocardial damage caused by COVID-19 is a sign of disease exacerbation.

Based on the close interaction between COVID-19 and CVD, can myocardial markers be used clinically as predictors of prognosis in COVID-19 patients? A study²² included 1099 COVID-19 patients from 552 hospitals in 31 provinces in China, and these patients were classified into severe and nonsevere groups according to the adult community-acquired pneumonia guidelines issued by the American Thoracic Association. Admission to the intensive care unit (ICU) for treatment, mechanical ventilation, and death were identified as the main composite endpoints of the study. The results of the study showed that myocardial injury markers (including lactate dehydrogenase [LDH] and creatinine kinase) were expressed at higher levels in critically ill patients and patients with major composite endpoint events than in nonsevere patients. In addition, in a family cluster of COVID-19 cases in Shenzhen, three of five patients with confirmed cases of COVID-19 had increased LDH levels (> 214 U/L); all three patients were older than 60 years, and their symptoms worsened after onset.²³ The first reported COVID-19 patient in the USA also showed increased LDH levels during hospitalization.²⁴ The aforementioned studies showed that troponin elevation likely reflects nonischaemic or secondary myocardial injury²³ and confirm that myocardial markers, especially high-sensitivity cardiac troponin, can be used as predictors of prognosis in COVID-19 patients.²⁵

Main impact of coronavirus disease 2019 on the cardiovascular system

Acute myocardial injury

Acute myocardial injury is defined as an increase in troponin protein I (TnI)/troponin T or a new abnormality detected by electrocardiogram and echocardiography. Clinical studies have shown that 7.2% to 23.0% of patients with COVID-19 have acute myocardial injury, mainly manifested as TnI levels above the 99th percentile reference upper limit or new abnormalities on electrocardiogram and echocardiogram.^{7,26–28} A clinical study involving 41 patients with COVID-19 pointed out that five (12%) patients had myocardial damage due to SARS-CoV-2 infection (serum TnI > 28 ng/L), of whom four patients were treated in the ICU, accounting for 31% of the total ICU patients.⁴ Another clinical study involving 138 COVID-19 patients also showed that the condition of patients with acute myocardial injury during infection is more likely to deteriorate, leading to admission to the ICU.⁷ These findings suggest that acute myocardial injury caused by SARS-CoV-2 infection is very common and may lead to severe clinical phenotypes or adverse endpoints in patients with COVID-19.²⁹

Arrhythmia

SARS-CoV, which caused a global epidemic in 2003, is related to SARS-CoV-2, which causes COVID-19.³⁰ Therefore, the two viruses may have similar effects on the heart. A report involving 121 patients with SARS showed that 87 patients (71.9%) developed tachycardia unrelated to fever during hospitalization, and nearly 40% of them continued to develop tachycardia even during follow-up; other arrhythmias included bradycardia (18 cases) and paroxysms of atrial fibrillation (one case).³¹ Similarly, in a study of 138 hospitalized COVID-19 patients, arrhythmias represented the leading complication (19.6%) after acute distress respiratory syndrome, occurring in 44.4% of ICU patients.³² COVID-19 patients with elevated troponin levels had a higher incidence of arrhythmia than those with normal troponin levels (11.5% vs. 5.2%, $P < 0.001$).²⁰ These studies suggested that arrhythmia may also be an important cardiac complication in patients with COVID-19. It is believed that myocardial damage might be a main driver of the enhanced risk of arrhythmia in these patients.³² In addition to participating in myocardial injury, inflammatory cytokines, especially IL-6, can directly promote QTc prolongation by regulating ion channels in cardiomyocytes and indirectly promote QTc prolongation by inhibiting CYP450-3A4 to increase the bioavailability of concomitant QT-prolonging drugs. In addition, inflammatory cytokines can induce the overactivation of the cardiac sympathetic

system and increase the electrical instability of the heart due to their direct stimulation of the autonomic nervous system.³³ In fact, some 'off-label' drugs used to combat viral invasion and replication may promote QTc prolongation.³⁴

Heart failure

A clinical study of 99 patients with confirmed cases of COVID-19 released by Wuhan Jinyintan Hospital showed that as of 25 January 2020, 11 (11%) of these patients had died, and patients infected with SARS-CoV-2 with no previous history of chronic heart disease can also experience severe heart failure and eventually die of sudden cardiac death.³⁵ With regard to heart failure reported in the literature, the possibility of cor pulmonale should be considered. Lung involvement in patients with COVID-19 can cause an imbalance in pulmonary ventilation perfusion and a reduction in the pulmonary vascular bed. The occlusion of microvessels and the reduction of functional residual capacity can lead to increases in pulmonary vascular resistance, which, in turn, cause pulmonary hypertension and pulmonary heart disease, eventually leading to right ventricular involvement and right heart failure. Although there are few reported cases of heart failure in COVID-19 patients, the importance of the clinical signs of heart failure should be emphasized.³⁶ Once the patient shows signs of heart failure, it should be treated promptly to reduce the case-fatality rate. Dyspnoea and fatigue are the two main symptoms of heart failure, and they are also very common in patients with COVID-19, especially the severe form.^{4,30} In addition, COVID-19 and heart failure can cause hypoxemia, which is the basic pathophysiological mechanism leading to death.³⁵ As a result, the diagnosis of chronic heart failure in COVID-19 patients has become more difficult and important.

Main mechanism of cardiovascular damage in coronavirus disease 2019

Destruction of the balance of the renin-angiotensin-aldosterone system

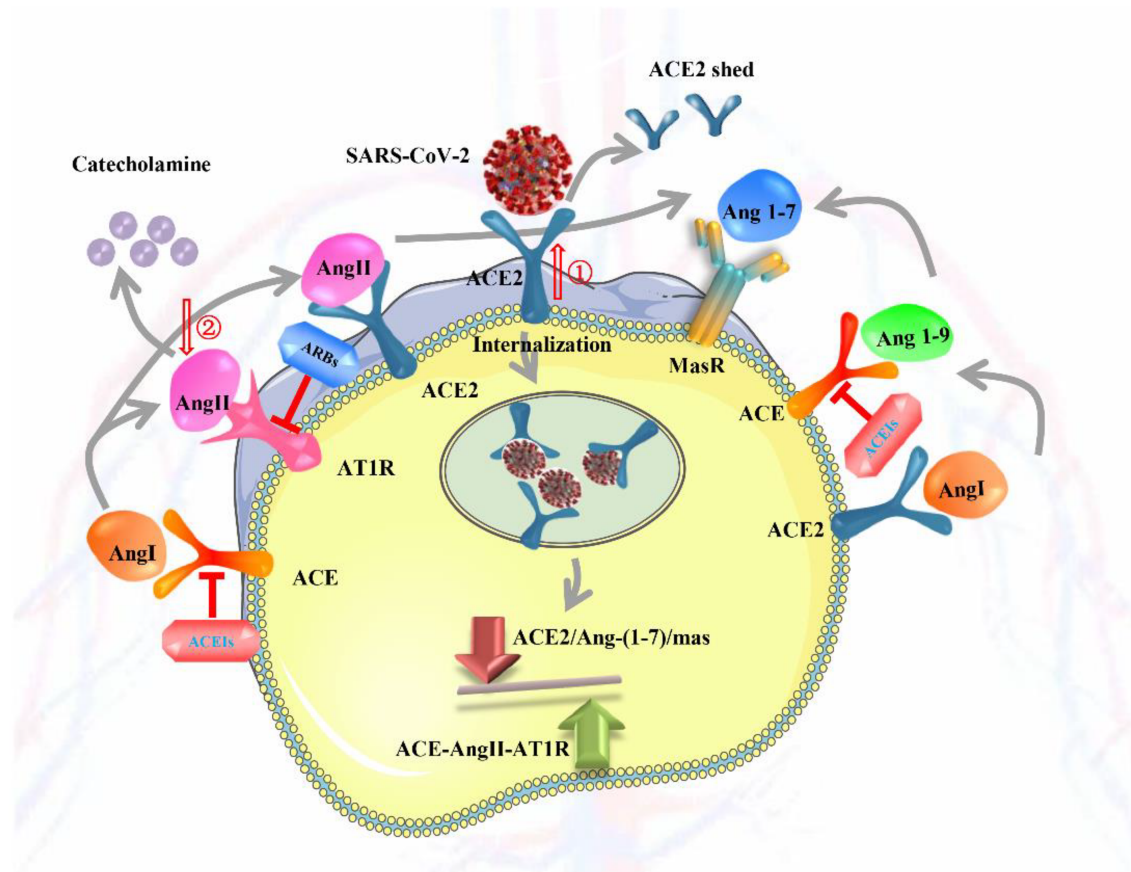
Previous studies confirmed that SARS-CoV enters the host cell after binding to ACE2 on the host cell surface with its S protein.³⁷ Based on single-cell sequencing data, Han's team found that the human organ expression level of ACE2 from high to low was the ileum, heart, kidney, bladder, oesophagus, lung, and trachea. The rate of positivity for ACE2 on myocardial cells is 7.5%.³⁸ Therefore, SARS-CoV-2 can enter cardiomyocytes through ACE2. The current study found that the mean systolic blood pressure (145 mmHg) of patients with COVID-19 who were in the ICU was higher than that of patients with COVID-19 (120 mmHg) who were not in the

ICU, which could suggest that severe illness may be related to the down-regulation of ACE2.⁴ Therefore, it is speculated that some patients with COVID-19 also have an imbalance in the renin-angiotensin-aldosterone system (RAAS). It is well known that ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are widely used to regulate the RAAS.

Therefore, it is unclear whether ACEIs/ARBs can be used in COVID-19 patients with co-morbid CVD³⁹⁻⁴¹ (Figure 1). There are currently three opinions on this topic in academic circles. One perspective is that RAAS inhibitors exert their protective effects by inhibiting the ACE-Ang II-AT1R axis and activating the ACE2/Ang-(1-7)/Mas pathway.⁴² The second view is that, on the one hand, ACEIs/ARBs can reduce the level of Ang II in the body,⁴³ prevent cytokine storms caused by the excessive activation of Ang II, and slow the progression of COVID-19 into the severe form.^{44,45} On the other hand, ACEIs/ARBs can improve the balance of the RAAS in COVID-19 patients

with CVD, alleviate the deterioration of CVD, and allow more time for the treatment of COVID-19.^{27,40,46,47} Another perspective is that the use of ACEIs/ARBs is not related to the severity of the disease. First, the gene for ACE2 is located on the X chromosome,⁴⁸ which means that men have half the amount of ACE2 as women, but men are actually at higher risk than women.⁴⁹ This observation shows that the amount of ACE2 is not necessarily positively related to the risk of SARS-CoV-2 infection. The occurrence of viral infection may be related to the amount of virus inhaled, the virulence of the virus, and the body's own immunity. In addition, ACE2 is widely distributed in multiple organs throughout the body, but the virus overwhelmingly invades the lung tissue and invades extrapulmonary tissue to a much lesser degree.⁴⁹ This further indicates that the amount of ACE2 is not positively correlated with the risk of infection; this is speculated to be mainly related to the deposition of the virus in the respiratory

Figure 1 Possible effects of ACEIs/ARBs on the renin-angiotensin-aldosterone system (RAAS) in patients with underlying cardiovascular diseases after SARS-CoV-2 infection. ① One view is that RAAS inhibitors may lead to an increased ACE2 reflex in patients with COVID-19, and SARS-CoV-2 infects humans by binding to ACE2. Therefore, the use of ACEIs/ARBs has the potential to accelerate viral replication or entrance into cells. ② The second view is that ACEIs/ARBs can reduce the level of Ang II in the body, prevent cytokine storms caused by the excessive activation of Ang II, and improve the balance of the RAAS in COVID-19 patients with cardiovascular disease. ③ Another view is that the use of ACEIs/ARBs is not related to the severity of the disease. ACE2, angiotensin-converting enzyme 2; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.



tract of the lung, while viraemia is less severe. Some recent authoritative studies have shown that previous treatment with ACEIs/ARBs did not increase the risk of SARS-CoV-2 infection or the likelihood of severe illness in COVID-19 patients.^{50,51} ACEIs/ARBs should not be discontinued to prevent a severe case of COVID-19.^{52,53} Prospective trials are needed to ascertain whether these drugs may have protective effects.⁵⁴

Cytokine storm

Previous studies have found that cytokine storms play a crucial role in the pathogenesis of SARS and MERS^{55–57} and may be related to cardiovascular complications associated with SARS-CoV infection.³¹ Similar to patients infected with SARS-CoV and MERS-CoV, those infected with SARS-CoV-2 can exhibit an enhanced Th1 response and the release of the corresponding inflammatory factors.²³ At the same time, the expression of interleukin (IL)-4 and IL-10 is also increased, which indicates that the Th2 response is enhanced.^{4,22} Cytokine storms cause the proliferation of highly pro-inflammatory CCR4+CCR6+Th17 cells, CD8+ T cells express high concentrations of cytotoxic particles, and the overactivation of T cells leads to stronger inflammatory storms.⁵⁸ A study involving 123 patients diagnosed with COVID-19 found that plasma levels of IL-6 and IL-10 were higher in patients with severe disease and that their CD4+ T and CD8+ T cells were lower than in patients with mild disease.⁵⁹ The other two studies reached the same conclusion.^{27,60} Therefore, the cytokine storm caused by SARS-CoV-2 infection may be one of the important mechanisms underlying myocardial injury.

Oxygen supply and demand imbalance

Hypoxemia, respiratory failure, shock, or hypotension induced by pulmonary infections can lead to insufficient oxygen supply to the myocardium. After infection, the body's metabolism increases, which increases the burden on the heart and then leads to an imbalance in the oxygen supply and demand in the body.⁶¹ The imbalance in the oxygen supply and demand in the body will cause the body to become hypoxic, increase anaerobic fermentation, and cause acidosis and the production of oxygen free radicals in the cell, thereby destroying the phospholipid layer of the cell membrane.^{62,63} As the duration of hypoxia increases, the intracellular calcium ion concentration increases significantly, leading to intracellular calcium overload and further causing myocardial cell damage. This phenomenon is more obvious in patients with chronic CVD, such as coronary heart disease and heart failure.^{64,65}

Side effects of treatment drugs

Clinical studies have confirmed the effects of chloroquine on arrhythmia caused by prolonged QT intervals, conduction disturbances, and increased autonomy.^{66,67} The clinical manifestations of chloroquine-induced cardiotoxicity are not specific, and one or more of the following abnormalities can appear^{68,69}: (i) cardiac conduction disorders; (ii) ventricular premature beats, sometimes in the doublet or triplet, occasionally atrial flutter or atrial fibrillation; and (iii) a history of ventricular fibrillation and cardiac arrest in individual cases. The dosage of and indication for chloroquine were specified in the COVID-19 protocol (trial seventh edition), and it was pointed out that additional data on adverse cardiac reactions were needed.

Psychological factors

SARS-CoV-2 infections, especially severe infections, can cause significant anxiety.⁷⁰ These physical and psychological stress processes lead to the release of large quantities of catecholamines, leading to direct myocardial damage.⁷¹

Underlying cardiovascular diseases

There is a high proportion of elderly patients among critically ill patients. Therefore, the chances of critically ill COVID-19 patients having co-morbid CVD are higher.²⁶ According to reports on clinical observations and research, approximately one-third of COVID-19 patients have hypertension and CVD.^{4,22} In this group of patients, SARS-CoV-2 infection aggravates the existing CVDs.

Treatment

Treatment of cardiovascular complications

Treatment is based on the correction of hypoxia, general treatment, and myocardial nutrition; there are additional appropriate treatments according to the type of arrhythmia. At the same time, clinicians should be alert to the occurrence of malignant arrhythmias.⁷² β -Receptor blockers can be given to reduce the heart rate. Patients with atrial fibrillation and supraventricular tachycardia can undergo cardioversion therapy. Those with tachycardia can immediately be given electrical cardioversion, beta-blockers, amiodarone, and sedative-induced hibernation. When concomitant heart failure requires the active correction of hypoxia, diuresis, and vasodilator treatment, positive inotropic drugs such as digitalis, dobutamine, and levosimendan can be given at the same time if necessary.

Treatment of coronavirus disease 2019

Remdesivir (GS-5734), an adenosine analogue, interferes with the action of viral RNA-dependent RNA polymerase through its active form, GS-441524, resulting in the reduced production of viral RNA. A recent double-blind, randomized, placebo-controlled trial of intravenous remdesivir treatment in 1063 COVID-19 patients showed that remdesivir can significantly reduce the recovery time of patients.⁷³ Another study showed no significant difference between the 5 day course and 10 day course of remdesivir in patients with severe COVID-19 who did not require mechanical ventilation. Unfortunately, there was no placebo control group in the study, so the magnitude of the effect of remdesivir is uncertain.⁷⁴

Lopinavir and ritonavir, protease inhibitors, are used to treat HIV infection. There are some suggestions that the use of lopinavir–ritonavir can shorten ICU stays and the time to hospital discharge.⁷⁵ However, a recent study including hospitalized adult patients with severe COVID-19 found no benefit with lopinavir–ritonavir treatment compared with standard care.⁷⁵ Therefore, the possibility of a treatment benefit needs further investigation in future trials.

Earlier studies suggested that chloroquine can effectively inhibit SARS-CoV-2 infection.⁷⁶ Therefore, chloroquine has been used as a clinical drug for the treatment of COVID-19. However, the role of hydroxychloroquine and chloroquine in the treatment of COVID-19 has been challenged by recent studies. A recent randomized trial showed that after high-risk or moderate-risk exposure to COVID-19, hydroxychloroquine had no preventive effect when used as postexposure prophylaxis within 4 days after exposure.⁷⁷ An observational study from a large medical centre in New York City found no association between hydroxychloroquine use and intubation or death.⁷⁸ An analysis of the World Health Organization

Pharmacovigilance Database described potentially lethal acute cardiac proarrhythmogenic effects leading to ventricular arrhythmias mainly with azithromycin but also with hydroxychloroquine, and the two have a synergistic effect.⁶⁷ In addition, the prolonged use of hydroxychloroquine was also associated with potentially lethal heart failure.⁶⁷

Conclusion and future directions

There is an interaction between COVID-19 and CVD. SARS-CoV-2 can cause CVD, including acute myocardial injury, arrhythmia, and heart failure, through a variety of pathways. COVID-19 patients with underlying CVD have a higher mortality rate. Therefore, close attention should be paid to cardiovascular complications during the diagnosis and treatment of COVID-19 to reduce the mortality of patients. At present, there is insufficient evidence that the use of ACEIs/ARBs aggravates the condition of COVID-19 patients. Therefore, it is not necessary to stop treatment with ACEIs/ARBs in CVD patients after SARS-CoV-2 infection.

Conflict of Interest

The authors declare that they have no competing financial interests.

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References

- Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, Zhong W, Hao P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; **63**: 457–460.
- Forni D, Cagliani R, Clerici M, Sironi M. Molecular evolution of human coronavirus genomes. *Trends Microbiol* 2017; **25**: 35–48.
- Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270–273.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497–506.
- Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020; **17**: 259–260.
- Akhmerov A, Marban E. COVID-19 and the heart. *Circ Res* 2020; **126**: 1443–1455.
- 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, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061.
- Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol* 2019; **16**: 203–212.
- Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol* 2019; **74**: 2529–2532.
- Association, HFGoCSoCoCM, Association, CHFAoCMD, Cardiology, EBoCJo. Chinese guidelines for the diagnosis and treatment of heart failure 2018.

- Zhonghua Xin Xue Guan Bing Za Zhi* 2018; **46**: 760–789.
11. Epidemiology Working Group for Ncjp Epidemic Response, Chinese Center for Disease Control Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 145–151.
 12. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor for Wuhan 2019-nCoV. *bioRxiv*. 2020: 2020.2001.2026.919985.
 13. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239.
 14. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, He MA, Cheng LX, Huang K, Zeng QT. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi* 2020; **48**: E004.
 15. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbicatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020; **41**: 1821–1829.
 16. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020; **116**: 1097–1100.
 17. Tucker NR, Chaffin M, Bedi KC, Papangelis I, Akkad AD, Arduini A, Hayat S, Eraslan G, Muus C, Bhattacharyya R, Stegmann CM, Margulies KB, Ellinor PT. Myocyte specific upregulation of ACE2 in cardiovascular disease: implications for SARS-CoV-2 mediated myocarditis. *medRxiv*. 2020.
 18. Li M, Dong Y, Wang H, Guo W, Zhou H, Zhang Z, Tian C, Du K, Zhu R, Wang L, Zhao L, Fan H, Luo S, Hu D. Cardiovascular disease potentially contributes to the progression and poor prognosis of COVID-19. *Nutr Metab Cardiovasc Dis* 2020; **30**: 1061–1067.
 19. Zhang J, Lu S, Wang X, Jia X, Li J, Lei H, Liu Z, Liao F, Ji M, Lv X, Kang J, Tian S, Ma J, Wu D, Gong Y, Xu Y, Dong W. Do underlying cardiovascular diseases have any impact on hospitalised patients with COVID-19? *Heart* 2020; **106**: 1148–1153.
 20. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 811.
 21. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; **5**: 802.
 22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for C. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–1720.
 23. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514–523.
 24. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, Spitters C, Ericson K, Wilkerson S, Tural A, Diaz G, Cohn A, Fox L, Patel A, Gerber SI, Kim L, Tong S, Lu X, Lindstrom S, Pallansch MA, Weldon WC, Biggs HM, Uyeki TM, Pillai SK, Washington State -nCoV VCIT. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020; **382**: 929–936.
 25. Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. *Circulation* 2020; **141**: 1733–1735.
 26. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; **8**: 475–481.
 27. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: E005.
 28. Liu M, He P, Liu HG, Wang XJ, Li FJ, Chen S, Lin J, Chen P, Liu JH, Li CH. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: E016.
 29. Lala A, Johnson KW, Russak AJ, Paranjpe I, Zhao S, Solani S, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Januzzi J, Mancini DM, Fuster V. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *medRxiv*. 2020.
 30. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 2020; **367**: 1260–1263.
 31. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GW, Soo YO, Chiu ML, Chan YS, Hui D, Lee N, Wu A, Leung CB, Sung JJ. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J* 2006; **82**: 140–144.
 32. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, Brown TS, Der Nigoghossian C, Zidar DA, Haythe J, Brodie D, Beckman JA, Kirtane AJ, Stone GW, Krumholz HM, Parikh SA. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol* 2020; **75**: 2352–2371.
 33. Lazzarini PE, Boutjdir M, Capecchi PL. COVID-19, arrhythmic risk and inflammation: mind the gap! *Circulation* 2020; **142**: 7–9.
 34. Gérard A, Romani S, Fresse A, Viard D, Parassol N, Granvullemin A, Chouchana L, Rocher F, Drici M-D. “Off-label” use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapies*. 2020. <https://doi.org/10.1016/j.therap.2020.05.002>
 35. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507–513.
 36. Han Y. Initial COVID-19 affecting cardiac patients in China. *Eur Heart J* 2020; **41**: 1719.
 37. Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Drosten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013; **495**: 251–254.
 38. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020; **14**: 185–192.
 39. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020; **63**: 364–374.

40. Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: E014.
41. de Simone G, Mancusi C. Speculation is not evidence: antihypertensive therapy and COVID-19. *Eur Heart J Cardiovasc Pharmacother* 2020; **6**: 133–134.
42. Callera GE, Antunes TT, Correa JW, Moorman D, Gutsol A, He Y, Cat AN, Briones AM, Montezano AC, Burns KD, Touyz RM. Differential renal effects of candesartan at high and ultra-high doses in diabetic mice—potential role of the ACE2/AT2R/Mas axis. *Biosci Rep* 2016; **36**: e00398.
43. Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Putko B, Kassiri Z, Turner AJ, Oudit GY. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. *J Mol Cell Cardiol* 2014; **66**: 167–176.
44. Soto M, Bang SI, McCombs J, Rodgers KE. Renin angiotensin system-modifying therapies are associated with improved pulmonary health. *Clin Diabetes Endocrinol* 2017; **3**: 6.
45. Caldeira D, Alarcao J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012; **345**: e4260.
46. 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, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; **11**: 875–879.
47. 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**: 586–590.
48. Burrell LM, Harrap SB, Velkoska E, Patel SK. The ACE2 gene: its potential as a functional candidate for cardiovascular disease. *Clin Sci (Lond)* 2013; **124**: 65–76.
49. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020; **92**: 577–583.
50. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020; **382**: 2441–2448.
51. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–angiotensin–aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020; **382**: 2431–2440.
52. de Abajo FJ, Rodriguez-Martin S, Lerma V, Mejia-Abril G, Aguilar M, Garcia-Luque A, Laredo L, Laosa O, Centeno-Soto GA, Angeles Galvez M, Puerro M, Gonzalez-Rojano E, Pedraza L, de Pablo I, Abad-Santos F, Rodriguez-Manas L, Gil M, Tobias A, Rodriguez-Miguel A, Rodriguez-Puyol D, group M-ACs. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020; **395**: 1705–1714.
53. Amat-Santos IJ, Santos-Martinez S, Lopez-Otero D, Nombela-Franco L, Gutierrez-Ibanes E, Del Valle R, Munoz-Garcia E, Jimenez-Diaz VA, Regueiro A, Gonzalez-Ferreiro R, Benito T, Sanmartin-Pena XC, Catala P, Rodriguez-Gabella T, Delgado-Arana JR, Carrasco-Moraleja M, Ibanez B, San Roman JA. Ramipril in high risk patients with COVID-19. *J Am Coll Cardiol* 2020; **76**: 268–276.
54. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID 19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020; **22**: 957–966.
55. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, Lit LC, Hui DS, Chan MH, Chung SS, Sung JJ. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004; **136**: 95–103.
56. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017; **39**: 529–539.
57. Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine* 2018; **104**: 8–13.
58. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420–422.
59. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, Lang C, Xiao Q, Xiao K, Yi Z, Qiang M, Xiang J, Zhang B, Chen Y. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *medRxiv*. 2020:2020.2002.2010.20021832.
60. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, Li W, Tong Q, Yi J, Zhao L, Xiong L, Guo C, Tian J, Luo J, Yao J, Pang R, Shen H, Peng C, Liu T, Zhang Q, Wu J, Xu L, Lu S, Wang B, Weng Z, Han C, Zhu H, Zhou R, Zhou H, Chen X, Ye P, Zhu B, Wang L, Zhou W, He S, He Y, Jie S, Wei P, Zhang J, Lu Y, Wang W, Zhang L, Li L, Zhou F, Wang J, Dittmer U, Lu M, Hu Y, Yang D, Zheng X. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine* 2020; **55**: 102763.
61. Biddlestone J, Bandarra D, Rocha S. The role of hypoxia in inflammatory disease (review). *Int J Mol Med* 2015; **35**: 859–869.
62. Werns SW, Lucchesi BR. Myocardial ischemia and reperfusion: the role of oxygen radicals in tissue injury. *Cardiovasc Drugs Ther* 1989; **2**: 761–769.
63. Cadenas S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. *Free Radic Biol Med* 2018; **117**: 76–89.
64. Durante W. Targeting endoplasmic reticulum stress in hypoxia-induced cardiac injury. *Vascul Pharmacol* 2016; **83**: 1–3.
65. Consolini AE, Ragone MI, Bonazzola P, Colareda GA. Mitochondrial bioenergetics during ischemia and reperfusion. *Adv Exp Med Biol* 2017; **982**: 141–167.
66. Desai KR, Dattani JJ, Rajput DK, Moid N, Highland HN, George LB. Role of curcumin on chloroquine phosphate-induced reproductive toxicity. *Drug Chem Toxicol* 2012; **35**: 184–191.
67. Nguyen LS, Dolladille C, Drici MD, Fenioux C, Alexandre J, Mira JP, Moslehi JJ, Roden DM, Funck-Brentano C, Salem JE. Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization Pharmacovigilance Database. *Circulation* 2020; **142**: 303–305.
68. pneumonia, mcgoDoSaToGPaHCoGPfcittonc. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; **43**: E019.
69. Li R, Yin K, Zhang K, Wang YY, Wu QP, Tang SB, Cheng JD. Application prospects of virtual autopsy in forensic pathological investigations on COVID-19. *Fa Yi Xue Za Zhi* 2020; **36**: 149–156.
70. Zhao Q, Hu C, Feng R, Yang Y. Investigation of the mental health of patients with novel coronavirus pneumonia. *Chinese Journal of Neurology* 2020. <http://rs.yiigle.com/yufabiao/1183762.htm>
71. DiBona GF. The sympathetic nervous system and hypertension: recent developments. *Hypertension* 2004; **43**: 147–150.
72. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol* 2020; **31**: 1003–1008.
73. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A,

- Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh M, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *N Engl J Med*. 2020. <https://doi.org/10.1056/nejmoa2007764>
74. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn M-Y, Nahass RG, Chen Y-S, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. 2020. <https://doi.org/10.1056/nejmoa2015301>
75. 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, Wang C. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; **382**: 1787–1799.
76. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**: 269–271.
77. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hultsiek KH. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020; **383**: 517–525.
78. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, Labella A, Manson DK, Kubin C, Barr RG, Sobieszczyk ME, Schluger NW. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020; **382**: 2411–2418.