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Review

Advances in the relationship between coronavirus infection and cardiovascular diseases

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has once again aroused people's concern about coronavirus. Seven human coronaviruses (HCoVs) have been discovered so far, including HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU115, severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus 2. Existing studies show that the cardiovascular disease increased the incidence and severity of coronavirus infection. At the same time, myocardial injury caused by coronavirus infection is one of the main factors contributing to poor prognosis. In this review, the recent clinical findings about the relationship between coronaviruses and cardiovascular diseases and the underlying pathophysiological mechanisms are discussed. This review aimed to provide assistance for the prevention and treatment of COVID-19.

1. Introduction

At the end of 2019, a number of patients with fever and clinical pneumonia of unknown origin were found in Wuhan, Hubei, China [1]. Through virus isolation, gene detection and the analysis of protein structure in the laboratories, the disease was identified as 2019 novel coronavirus pneumonia caused by a new kind of coronavirus. Researchers have found that this new coronavirus belongs to the severe acute respiratory syndrome coronavirus (SARS-CoV) [2–4]. This novel coronavirus is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On February 12, 2020, the World Health Organization (WHO) announced that the disease caused by SARS-CoV-2 was officially named "coronavirus disease 2019" (COVID-19). COVID-19 is another serious infectious disease caused by coronavirus after severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2015. SARS-CoV-2 is the seventh member of the coronavirus family to infect humans [1].

Since January 2020, COVID-19 has rapidly spread throughout China, causing serious harm to human health. Up to April 27, 2020, at least 2,878,196 patients have been confirmed to have COVID-19 all over the world, of whom 198,668 have died [5]. The WHO characterized COVID-19 as a pandemic on March 11, 2020, after it announced that COVID-19 in China was a public health emergency of international concern (PHEIC) on January 31, 2020 [6,7]. Due to the severe outbreak of COVID-19 and its wide-ranging scope, strict prevention and control strategies should be implemented in the affected countries, and the treatment of infected individuals should receive more attention.

As reported by the China Centers for Disease Control and Prevention, approximately 12.8 % of patients with COVID-19 have hypertension, and 4% of patients have cardiovascular disease (CVD). The mortality rate of patients with cardiovascular disease is much higher than that of patients without comorbidities [8]. Growing evidence suggests that combined cardiovascular disease may increase the severity of coronavirus infection and lead to a poor prognosis [9–13]. At the same time, there is also evidence suggesting that serum levels of cardiac necrosis biomarkers have increased to varying degrees in both mild and severe COVID-19 patients, suggesting different degrees of myocardial damage [9–14]. Moreover, the study found that the markers of myocardial necrosis in severe and deceased COVID-19 patients were significantly higher than those in mild COVID-19 patients, suggesting that cardiac damage may be related to poor prognosis [9,10,12,13]. Existing evidence suggests that COVID-19 is closely related to cardiovascular disease, but the specific interaction between the two is unclear. This paper describes the relationship between coronavirus and

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cardiovascular diseases through a review of the literature and datasets about SARS, MERS and other diseases caused by the human coronavirus, hoping to provide some assistance for the prevention and treatment of COVID-19.

2. Human coronavirus

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes the Coronaviridae, Arteriviridae, and Roniviridae families. CoVs are further subdivided into four groups, the α, β, γ, and δ CoVs [15]. The newly discovered SARS-CoV-2 belongs to the β-CoVs [2]. All CoVs are enveloped, nonsegmented positive-sense RNA viruses [15]. The most significant feature of CoVs is the club-shaped spike projections emanating from the surface of the virion. Therefore, CoV look like a tiny corona, as depicted in studies by cryo-electron tomography and cryo-electron microscopy, prompting the name coronavirus [16–18]. CoV is a respiratory virus that exists widely in nature. Its natural hosts include humans and other mammals, such as pigs, dogs, cats, mice, and bats [19].

At present, seven human coronaviruses (HCoVs) have been discovered, in which HCoV-229E [20], HCoV-NL63 [21,22], HCoV-OC43 [23–25], HCoV-HKU1 [26], SARS-CoV [27–30] and MERS-CoV [31,32] are included, in addition to SARS-CoV-2 recently isolated from the respiratory tracts of patients with COVID-19 in Wuhan [2–4]. HCoVs mainly cause respiratory infections, of which four endemic HCoVs (HCoV-NL63, HCoV-229E, HCoV-OC43, and HCoV-HKU1) mainly cause mild respiratory infections, and the other three epidemic HCoVs (SARS-CoV, MERS-CoV, SARS-CoV-2) can cause acute severe pneumonia [19,33].

Coronaviruses originally discovered as HCoV-229E are the cause of respiratory infections in children and adults, but they are not particularly dangerous. Patients' respiratory symptoms are mild, similar to those of the common cold [34]. Most clinically significant coronavirus infections occur in children under two years of age, although adults can also be severely infected [35,36]. Mortality is negligible [37]. However, SARS-CoV and MERS-CoV, which have appeared since 2003, are highly contagious and cause a high incidence and mortality rate of pneumonia [33,37–39]. In addition to SARS-CoV and MERS-CoV, SARS-CoV-2 is another human coronavirus that can cause severe pneumonia [1]. The researchers compared the sequence of SARS-CoV-2 from Wuhan with that of SARS-CoV and MERS-CoV through genetic testing and found that the gene sequence of SARS-CoV-2 is almost identical, with a homology to MERS of approximately 40 % and a higher degree of homology to SARS of approximately 70 % [40]. The differences between the sequences are mainly in the ORF1a gene and the spike gene, encoding S-protein, which is the key protein for the interaction between coronavirus and host cells [40].

The coronavirus spike protein is a multifunctional molecular machine that mediates coronavirus entry into host cells. It first binds to a receptor on the host cell surface through its S1 subunit and then fuses viral and host membranes through its S2 subunit [41,42]. Some cellular receptors of human coronavirus have been identified, including angiotensin-converting enzyme 2 (ACE2) [40,43,44], dipeptidyl peptidase 4 (DPP4) [45] and aminopeptidase N (APN) [46]. Coronavirus enters the human body through receptors on the surface of host cells, multiplies in the body, and causes inflammation in the body and diseases such as pneumonia.

3. ACE2

Similar to SARS-CoV, ACE2 was found to be a receptor for SARS-CoV-2 [43,47,48]. ACE2 is also an important member of the renin-angiotensin-aldosterone system (RAAS). It catalyzes the conversion of angiotensin II (Ang II) to angiotensin 1−7, activates downstream Mas receptors, and finally exerts anti-inflammatory and antiproliferative effects [49]. In addition, ACE2 can also decompose Ang II into angiotensin 1–9. Angiotensin 1–9 not only can be catalyzed by ACE and further decompose into angiotensin 1−7 but also can directly activate Ang II type 2 receptor (AT2R), exerting its anti-inflammatory and anti-angiotensin II type 1 receptor (AT1R) effects [50].

ACE2 is primarily expressed in the heart, kidneys, and testes, and it is widely distributed in human alveolar epithelial cells, small intestinal epithelial cells, arterial smooth muscle and endothelial cells, and vein endothelial cells [51,52]. In the heart, ACE2 is expressed in the endothelium [51] and cardiomyocytes [53]. Increasing evidence suggests that ACE2 enzyme activity has a protective role in cardiovascular disease. The loss of ACE2 can be harmful because it may lead to worsened heart function and the progression of heart and vascular disease [49,54]. Virus-induced ACE2 down regulation may attenuate its function, diminish its anti-inflammatory role, and heightened angiotensin II effects in the predisposed patients [55]. The tissue localization of the receptors correlates with COVID-19 presenting symptoms and organ dysfunction. In the lung, ACE2 is expressed in type I and type II alveolar epithelial cells. In addition, 83 % of type II alveolar cells express ACE2 [56]. The combination of SARS-CoV-2 with ACE2 results in increased expression of ACE2, which can lead to alveolar cell damage, in turn triggering a series of whole-body reactions and even death [48].

Wrapp et al. [18] found that the receptor-binding ability of SARS-CoV-2 is 10–20 times stronger than that of SARS-CoV, providing a laboratory basis to prove that SARS-CoV-2 is more infectious than SARS-CoV [3]. There is evidence showing that ACE2 levels are higher in men than in women [48]. However, the male-to-female ratio of NCP-confirmed cases is 0.99:1 in Wuhan, 1.04:1 in Hubei Province, and 1.06:1 in China [8], meaning that there are few differences in prevalence between men and women. However, the crude case fatality rate for men (2.8 %) is slightly higher than that for women (1.7 %) [8]. However, the relationship between ACE2 expression level and SARS-CoV-2 infection rate and mortality remains unclear.

RAAS inhibitors, including angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drugs, are commonly used in the treatment of hypertension, heart failure, and myocardial inflammation. They can control the level of Ang II in the body, slow down the deterioration of inflammation, and improve patient survival. ACEIs and ARBs can also exert their protective effects by activating the ACE2/angiotensin 1−7/Mas axis, which may lead to increased ACE2 in patients [57,58]. Increased ACE2 expression levels may lead to an increased risk of infection. However, there are no reports indicating that patients using ACEIs/ARBs are more likely to become infected. Whether ACEI / ARB can be widely used in COVID-19 patients with comorbid cardiovascular disease was unclear or even controversial [59]. But recently, Guo et al. reported that although more patients with higher troponin T (TnT) were using ACEI and ARB medications owing to their baseline CVD, their use was not associated with patients' mortality rate [60]. A research published in Circulation Research by Zhang et al. showed that Among hospitalized COVID-19 patients with hypertension, inpatient use of ACEI / ARB was associated with lower risk of all-cause mortality compared with ACEI / ARB non-users [61]. We can see that in-hospital use of ACEI / ARB was not associated with an increased mortality risk. There is no need for patients with hypertension to stop using ACEI / ARB or switch to other antihypertensive medicine.

4. Coronavirus and CVD

4.1. HCoV-229E, HKU1, NL63, and OC43 and CVD

HCoV-229E and HCoV-OC43 [35] were discovered in the 1960s, and HCoV-NL63 [22] and HCoV-HKU1 [26] were later discovered in upper respiratory tract infections, asthma, bronchiolitis, and pneumonia. There is evidence showing that infant, elderly and immunocompromised patients are more likely to be infected with high mortality rates [37,62–64]. These infected patients are more likely develop severe disease states [65–68].

Table 1
Underlying CVD in HCoV Infection.

HCoV	Authors and Research types			Study Region	Study Period	Case Size	Underlying CVD	Major Findings
229E, HKU1, NL63, OC43	Varghese et al. [37]	multicenter	retrospective	New York	1/2013～12/2014	261	congenital heart disease (CHD)	16.5 % of patients had CHD, and they were more likely to enter the PICU.
	TK, C et al. [69]	multicenter	retrospective	Sao Paulo	6/2001～9/2010	1137	CHD	17.3 % of patients had CHD
	Lee et al. [70]	single-center	retrospective	Saint Louis	12/2012～12/2013	4315	CHD	17.7 % of patients with CoV infections had congenital heart disease; CHD is a risk factor for adverse outcomes
SARS	Chen et al. [89]	single-center	retrospective	Taipei	3/2003～5/2003	67	hypertension; cerebrovascular disease	a risk factor for ARDS development.
	Wong et al. [88]	single-center	retrospective	Taipei	3/2003～5/2003	8	hypertension; coronary artery disease	60 % of deceased patients had hypertension, coronary artery disease or other comorbid conditions
	Chan et al. [86]	single-center	prospective	Hongkong	3/2003～6/2003	115	cardiac disease	a risk factor for adverse outcomes
	Tsang et al. [87]	single-center	retrospective	Hongkong	2/2003～3/2003	10	heart disease	a risk factor for mortality
	Hu et al. [90]	multicenter	retrospective	Beijing	5/2003～12/2003	1291	cardiovascular and cerebrovascular disease	People with cardiovascular and cerebrovascular diseases were 1.83 times more likely to die than those without underlying diseases
MERS	Assiri et al. [105]	multicenter	retrospective	Saudi Arabia	9/2012～6/2013	47	hypertension; chronic cardiac disease	34 % of patients had hypertension; 28 % had other chronic cardiac diseases.
	Jaffar et al. [106]	single-center	retrospective	Saudi Arabia	4/2013～6/2013	17	cardiac disease	53 % of patients had cardiac disease.
	A, B.et al. [107]	multicenter	meta-analysis	Saudi Arabia	2013～2016	637	hypertension; heart disease	50 % of patients had hypertension; 30 % of patients had heart disease.
	Garout et al. [108]	single-center	retrospective	Saudi Arabia	3/2014～7/2014	52	hypertension	51.9 % of patients had hypertension.
SARS-CoV-2	CDC [8]	multicenter	retrospective	China	12/2019～2/2020	44,672	hypertension; other CVD	15.7 % of deceased patients had hypertension, and 9% had other cardiovascular diseases
	Huang et al. [9]	multicenter	prospectively	Wuhan	12/2019～1/2020	41	hypertension; other CVD	15 % of patients with COVID-19 had hypertension, and 15 % had other CVDs.
	Wang et al. [10]	single-center	retrospective	Wuhan	1/2020～2/2020	138	hypertension; other CVD	31.2 % of patients with COVID-19 had hypertension, and 14.5 % had other CVDs.
	Chen et al. [11]	single-center	retrospective	Wuhan	1/1/2020～20/1/20020	99	cardiovascular and cerebrovascular disease	40 % of patients had cardiovascular and cerebrovascular disease.
	Yang et al. [12]	single-center	retrospective	Wuhan	12/2019～1/2020	52	chronic heart disease	10 % of patients had chronic heart disease and were more likely to die.
	Li et al. [13]	single-center	retrospective	Wuhan	1/2020～2/2020	25	hypertension; heart disease	64 % of deceased patients had hypertension and 32 % had heart disease.
	Li et al. [119]	multicenter	meta-analysis	China	12/2019～3/2020	1527	hypertension; cerebrovascular disease	17.1 % of patients with COVID-19 had hypertension and 16.4 % had cardia-cerebrovascular disease. The incidences of hypertension and cardia-cerebrovascular diseases were approximately two-fold and three-fold higher, respectively, in patients in the ICU with severe cases than in their non-ICU/severe case counterparts.
	Zhang et al. [132]	multicenter	retrospective	Wuhan	12/2019～3/2020	82	hypertension; heart disease; cerebrovascular disease	56.1 % of deceased patients had hypertension, 20.7 % had heart disease, 12.2 % had cerebrovascular disease.

Abbreviation: CDC: Chinese Center for Disease Control and Prevention; PICU: pediatric intensive care unit; ICU: intensive care unit.

Table 2
CVD Complication of HCoV infection.

HCoV	Authors and Research types			Study Region	Study Period	Case Size	CVD Complication	Abnormal Indicator	Major Findings
OC43	Lee et al. [70]	single-center	retrospective	Saint Louis	12/2012～12/2013	4315	hypotension	Blood pressure	Hypotension was found in a small number of patients with CoV infection.
SARS	Yu et al. [92]	multicenter	retrospective	America	2003	121	hypotension; tachycardia; bradycardia; cardiomegaly; cardiac arrhythmia	Blood pressure; heart rate	hypotension and tachycardia are common in SARS patients. Bradycardia and cardiac hypertrophy are less common, and arrhythmias are rare.
	Li et al. [91]	single-center	prospectively	Hongkong	2003	46	cardiac injury; diastolic impairment	CK; LDH; echocardiogram	SARS patients had subclinical diastolic impairment without contraction involvement, and this damage may be reversible upon clinical recovery.
	Yin et al. [94]	…	review	…	2018	…	vasculitis	…	SARS-CoV also attacks small blood vessels throughout the body, causing systemic vasculitis.
	Oudit et al. [99]	single-center	retrospective	Toronto	2013	20	myocardial damage	…	Decreased ACE2 expression may be responsible for the myocardial dysfunction and adverse cardiac outcomes in patients with SARS.
MERS	Alhogbani et al. [110]	…	case report	Saudi Arabia	2016	1	myocarditis; heart failure	hs-TnI; echocardiogram	This was the first case to show that MERS coronavirus may cause acute myocarditis and acute heart failure.
SARS-CoV-2	Huang et al. [9]	multicenter	prospectively	Wuhan	12/2019～1/2020	41	cardiac injury	hs-TnI	The levels of hs-CTnI of 5 patients increased significantly after infection
	Wang et al. [10]	single-center	retrospective	Wuhan	1/2020～2/2020	138	cardiac injury	CKMB; LDH; hs-TnI	10.2 % patients had acute cardiac injury
	Li et al. [124]	multicenter	meta-analysis	China	1/2020～3/2020	1527	cardiac injury	…	At least 8% of patients with COVID-19 suffered acute cardiac injury
	Wang et al. [125]	single-center	retrospective	Wuhan	1/2020～2/2020	53	tachycardia; electrocardiography abnormities; diastolic dysfunction; elevated myocardial enzymes; acute myocardial injury	Heart rate; CRP; D-dimer	15 of the 53 patients had tachycardia, 11 had electrocardiography abnormities, 20 had diastolic dysfunction, 30 had elevated myocardial enzymes and 6 had acute myocardial injury.
	Yang et al. [12]	single-center	retrospective	Wuhan	12/2019～1/2020	52	cardiac injury	hs-TnI	The level of hs-TnI is higher in severe infections.
	Li et al. [13]	single-center	retrospective	Wuhan	1/2020～2/2020	25	cardiac injury	hs-TnI; proBNP	The risk of heart injury in deceased patients is higher than that in survivors. 94.7 % patients' serum hs-TnI or/and proBNP levels were increased.
	Wu et al. [131]	single-center	retrospective	Wuhan	12/2019～1/2020	188	heart injury	hs-TnI; CRP; IL-6; lymphocytes	Hs-TnI at admission may be associated with increased mortality.
	Zhang et al. [132]	multicenter	retrospective	Wuhan	12/2019～3/2020	82	cardiac injury	hs-TnI; CRP; IL-6	89 % of deceased patients had cardiac injury. cardiac damage may have something to do with the cytokine storm resulting from an overaggressive host immune response.
	Lippi et al. [133]	multicenter	meta-analysis	China	12/2019～3/2020	…	cardiac injury	hs-TnI	Hs-TnI was 2.2-fold higher in ICU patients than in patients with mild cases.
	Liu et al. [134]	single-center	retrospective	Wuhan	12/2019～3/2020	291	cardiac injury	hs-TnI; proBNP	Patients in the ICU had much higher troponin I and NT-proBNP than the patients not in the ICU.
	Gao et al. [135]	single-center	retrospective	Wuhan	12/2019～3/2020	102	cardiac injury	proBNP	Patients with higher levels of proBNP had a higher risk of hospital death.
	Guo et al. [60]	Single-center	retrospective	Wuhan	30/1～30/2/2020	187	cardiac injury	TnT; proBNP	Myocardial injury is significantly associated with fatal outcome of COVID-19; Myocardial injury is associated with cardiac dysfunction and arrhythmias; Inflammation may be a potential mechanism for myocardial injury.
	Shi et al. [136]	Single-center	retrospective	Wuhan	20/1～10/2/2020	416	cardiac injury	hs-TNI; CK-MB; myohemoglobin	Cardiac injury is a common condition among hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality.

Abbreviation: CK, creatine kinase; LDH, lactate dehydrogenase; hs-TnI, hypersensitive troponin I; CKMB, creatine kinase-myocardial band isoenzyme; proBNP, pro brain natriuretic peptide; CRP, C-reactive protein; IL, Interleukin; TnT, troponin T.

Varghese et al. [37] retrospectively analyzed the clinical data of 261 children with HCoV infection (including 229E, HKU1, NL63, OC43) and found that approximately 16.5 % of the children had cardiovascular disease. HCoV-infected children with cardiovascular disease are more likely to receive respiratory support and enter a pediatric intensive care unit (PICU), suggesting that the underlying cardiovascular disease increased the severity of HCoV infection in the children. Cabeça et al. found that children with heart disease are more likely to be infected by HCoVs [69]. The presence of congenital heart disease was a significant risk factor for severe coronavirus infection in children who were less than five years old [70] (Table 1).

Hypotension was found in a small number of patients with these four HCoV infections [70] (Table 2). There is no relevant evidence showing that HCoV infection can cause heart injury. However, Kim et al. reported that HCoVs were detected in children with Kawasaki disease, which is characterized by acute systemic vasculitis in childhood and may induce severe cardiovascular complications [71]. Serological tests suggest that HCoV-229E may be involved in the occurrence of Kawasaki disease [72]. Therefore, we still need to pay attention to cardiovascular complications when facing these four kinds of HCoV infection.

4.2. SARS-CoV and CVD

The severe acute respiratory syndrome [27] that broke out globally in 2003 is different from the human coronavirus described previously. It is a severe acute respiratory infection with clinical manifestations of fever and dry cough, with the lungs as the main locations of lesions. Some patients quickly develop acute respiratory distress syndrome (ARDS) and multiple organ failure with high mortality [73–77].

There is much relevant evidence showing that pre-existing comorbid conditions are one of the major determinants of fatality [76,78–83]. It has been reported that the presence of cardiovascular diseases, such as hypertension and heart disease, is associated with adverse outcomes and mortality in SARS patients [84–87]. Wong et al. reviewed the medical records of fatal cases and found that 60 % of the patients who died had comorbid conditions such as hypertension and coronary artery disease [88]. Chen et al. found that patients with combined hypertension and cerebrovascular diseases are more likely to develop ARDS [89]. Another study by Hu et al. showed that the incidence rates of critical conditions and multiple organ dysfunction syndrome (MODS) among SARS patients with cardiovascular and cerebrovascular diseases were 1.8-fold and 1.9-fold higher than those of patients without underlying disease, suggesting that cardiovascular and cerebrovascular diseases are major risk factors for SARS patients to devolve into critical conditions and MODS and eventually lead to death [90] (Table 1).

Regarding the cardiovascular complications of SARS patients, it was found that SARS patients had subclinical diastolic impairment without contraction involvement, and this damage may be reversible upon clinical recovery [91]. Another study by Yu et al. found that cardiovascular complications, including hypotension and tachycardia, are common in SARS patients but are usually self-limiting. Bradycardia and cardiac hypertrophy were less common, and arrhythmias were rare [92]. Acute myocardial infarction can also be seen in a few SARS patients [93]. SARS-CoV was reported to be found in 40 % (7/18 patients) of heart samples from patients who died of SARS during the Toronto outbreak [76], which might explain the myocardial damage discovered in SARS patients [89]. There are reports indicating that SARS-CoV also attacks small blood vessels throughout the body, causing systemic vasculitis [94] (Table 2). In addition to clinical studies, laboratory studies were performed to look for the pathophysiological mechanism associated with myocardial dysfunction caused by SARS-CoV infection [95–99]. It was reported that pulmonary infection with SARS-CoV in mice led to a myocardial infection with a marked decrease in ACE2 expression, which may be responsible for the myocardial dysfunction and adverse cardiac outcomes in patients with SARS [99].

4.3. MERS-CoV and CVD

MERS is a severe respiratory infectious disease caused by MERS-CoV that was first reported in Saudi Arabia in September 2012 [29]. The symptoms are similar to those of SARS, and severe cases can manifest as pneumonia with ARDS and other severe life-threatening complications, such as septic shock, acute myocarditis and multiple organ failure [100–105]. The mortality rate of MERS is 35.5 %, which is much higher than that of SARS (10 %) [39].

It has been reported that people with underlying diseases such as diabetes, cardiovascular disease, renal failure, obesity, and immune deficiency are more likely to develop severe diseases after being infected with MERS-CoV [105,106]. Badawi et al. found that 50 % of MERS patients have diabetes and hypertension and that approximately 30 % of patients have heart disease [107]. They believed that these underlying disease conditions inhibit the synthesis of proinflammatory cytokines, damage the host's natural and humoral immune systems, and lead to an increased risk of severe MERS complications. Another study found that 46.2 % of the patients who died had hypertension, suggesting that the presence of underlying cardiovascular disease increased the mortality of MERS [108]. Banik suggested that sufficient attention should be paid to MERS patients with combined underlying diseases to reduce the occurrence of serious complications and mortality [109] (Table 1).

Heart damage was also reported in MERS patients [110]. MERS-CoV was found in the kidneys of deceased patients but was not detected in the heart tissue, and the heart showed no significant histological changes [111,112]. However, an animal model study clearly stated that MERS-CoV RNA could be seen in cardiac tissue, implying direct cardiac pathology [113]. The mechanism of heart injury in MERS infection remains unclear and requires more research.

4.4. SARS-CoV-2 and CVD

COVID-19, which broke out at the end of 2019, is a disease caused by infection with SARS-CoV-2 [1,2,4]. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 is a β-CoV [2]. COVID-19 is similar to SARS and MERS and manifests as extensively pathological viral lung inflammation [1]. Although similar to SARS-CoV and MERS-CoV, SARS-CoV-2 has its own characteristics [1,114]. Early cases suggest that COVID-19 may not be as severe as SARS and MERS. However, the rapidly increasing number of cases and increasing evidence of human-to-human transmission suggest that SARS-CoV-2 is more contagious than SARS-CoV and MERS-CoV and has a lower fatality [3,9,115–117]. Up to April 27, 2020, the overall mortality of COVID-19 was 6.9 % globally [5]. But the fatality rate is different in different regions and times, ranging from 0.7%–13.5 % [5,118].

The symptoms of COVID-19 infection appear after an incubation period of approximately 6.4 days [119]. Fever, fatigue, and dry cough are the main manifestations of COVID-19, and a few patients have symptoms such as nasal congestion, runny nose, sore throat, and diarrhea [2,9,120,121]. Patients with severe cases often experience dyspnea and/or hypoxemia one week after onset [122]. Severe cases of COVID-19 progress rapidly to acute respiratory distress syndrome, septic shock, and metabolic acidosis, which is difficult to correct, and coagulopathy [10].

Current case reports show that SARS-CoV-2 infection may have cardiovascular symptoms in addition to the typical respiratory symptoms. A small number of patients have atypical clinical manifestations and may start with cardiovascular symptoms such as chest tightness, palpitations and chest pain. A study by Liu et al. found that 7.3 % (10/137) of patients had palpitations as the first symptom [123]. It was also reported that 2% of patients experienced chest pain during hospitalization [11]. In addition, Wang et al. found that 16.7 % of patients with

COVID-19 had arrhythmias [10].

According to relevant studies [9–11,124], the proportion of COVID-19 patients with comorbid CVDs, such as hypertension, coronary artery disease and cerebrovascular disease, was larger than that of patients with other comorbidities or without comorbidities, suggesting that patients with CVD may be more susceptible to SARS-CoV-2 infection. Moreover, the incidence of CVD in patients with severe or fatal cases with COVID-19 was higher than that in patients with nonsevere cases or in those who survived [12,13,124]. According to the reports of the Chinese Center for Disease Control and Prevention, 15.7 % of the deaths were hypertension, and 9% had other cardiovascular diseases, further suggesting that underlying cardiovascular diseases may be one of the important risk factors for poor prognosis in patients with COVID-19 [8]. It can be seen not only that the number of COVID-19 patients with cardiovascular disease is large but also that these patients have poor tolerance to severe pneumonia and are more likely to develop severe cases (Table 1).

Cardiac complications such as electrocardiography abnormities, diastolic dysfunction, and acute myocardial injury were reported in patients with COVID-19 [124–127]. Cases of severe myocarditis with reduced systolic function have been reported after COVID-19 [128–130]. And SARS-CoV-2 infection-related myocarditis is likely associated with myocardial injury [60,128]. According to the study by Li et al., the most common organ damage outside the lungs was heart injury [13]. Serum myocardial necrosis markers such as hypersensitive troponin I (Hs-TnI) and creatine kinase (CK) increased to varying degrees in patients with mild and severe cases of COVID-19 [9–14,131–134]. However, the risk of heart injury was higher in patients with severe cases, approximately 22.2%–31% [9,12,126,133,134], than in patients with mild cases, approximately 2%–4% [9,10]. The percentage of heart injury in COVID-19 patients who died, approximately 28%–89% [12,13,132], was higher than that in those who survived. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were also reported to be increased [13,134,135]. Increased Hs-TnI and proBNP expression levels may be risk factors for severe illness and high mortality of COVID-19 [133–135]. Furthermore, it was found that high Hs-TnI levels were associated with increased levels of inflammation (neutrophils, IL-6, CRP, and PCT) and decreased levels of immunity (lymphocytes, monocytes, and CD4+ and CD8 + T cells), suggesting that cardiac injury may have something to do with the cytokine storm resulting from an overaggressive host immune response [131,132] (Table 2).

Two recent studies published in JAMA Cardiology reported the cardiovascular complications of COVID-19 in detail [60,136]. Shi et al. found that cardiac injury was a common condition among hospitalized patients with COVID-19 in Wuhan, China, and it is associated with higher risk of in-hospital mortality [136]. Guo et al. reported that Myocardial injury was significantly associated with fatal outcome of COVID-19. Myocardial injury was associated with cardiac dysfunction and arrhythmias. Inflammation may be a potential mechanism for myocardial injury [60] (Table 2).

COVID-19 may induce new cardiovascular diseases and / or aggravate potential cardiovascular diseases. The short-term and long-term cardiovascular effects of COVID-19 and the effects of specific treatments are unclear and need further investigation.

4.5. SARS-CoV-2 subtypes and CVD

As the epidemic spread, SARS-CoV-2 evolved multiple subtypes. In a recent study, researchers proposed the subdivision of the global SARS-CoV-2 population into sixteen well-defined subtypes by focusing on the widely shared polymorphisms in nonstructural (nsp3, nsp4, nsp6, nsp12, nsp13 and nsp14) cistrons, structural (spike and nucleocapsid) and accessory (ORF8) genes [137]. Six virus subtypes were predominant in the population, accounting for more than 97 % of the samples isolated from around the world. And the subtypes showed some geographical structure with two clusters: a smaller one comprised of isolates mostly sampled from Western hemisphere (Subtypes II, VI, IX, X and XI) and a larger one whose isolates were sampled from Western and Eastern hemispheres (Subtypes I, III, IV, V, VII, VIII, XII, XIII, XIV, XV and XVI) [137]. The researchers believed that the genetic structure determined for the SARS-CoV-2 population provides substantial guidelines for maximizing the effectiveness of trials for testing the candidate vaccines or drugs [137].

In another earlier study, population genetic analyses of 103 SARS-CoV-2 genomes indicated that these viruses evolved into two major types (designated L and S), that are well defined by two different single nucleotide polymorphisms (SNPs) [138]. The L type (~70 %) is more prevalent than the S type (~30 %), but the S type was found to be the ancestral version. The L type is more aggressive and spread more quickly. And it was more prevalent in the early stages of the outbreak in Wuhan. But the frequency of the L type decreased after early January 2020 for more severe selective pressure placed by human intervention on the L type [138]. Contrary to the L type, the S-type, which is evolutionarily older and less aggressive, might have increased in relative frequency due to the weaker selective pressure [138].

It was also reported that among the 27 viruses isolated from Wuhan, 26 (96.3 %) were L type, and only 1 (3.7 %) was S type [138]. However, among the other 73 viruses isolated outside Wuhan, 45 (61.6 %) were L type, and 28 (38.4 %) were S type [138]. This comparison suggests that the L type was significantly more prevalent in Wuhan than in other places. And recent studies about the clinical characteristics and outcomes of patients with COVID-19 in Wuhan [9–11,139] or outside Wuhan [134,140,141]have showed that the mortality of COVID-19 patients and the proportion of patients with cardiac injury outside Wuhan was lower than that in Wuhan (Table 3). Although there were many reasons for the different incidence of cardiac injury and outcome of COVID-19 in and outside Wuhan, such as the shortage of medical resources in Wuhan, the role of different SARS-CoV-2 subtypes cannot be ignored. The relationship between SARS-CoV-2 subtypes and the mortality of COVID-19 or the CVD complications need for further immediate, comprehensive studies that combine genomic data, epidemiological data, and records of the clinical symptoms of patients with coronavirus disease 2019.

5. Possible mechanisms underlying the increased susceptibility and severity of SARS-CoV-2 infection in patients with CVD

According to the references above, we can see that patients with underlying CVD may be more likely to become infected with coronavirus, and CVD may be one of the risk factors for poor prognosis and high mortality of CoV infection. Few studies, however, have explored the mechanisms underlying these associations. We believe that the possible mechanisms may be related to inflammation.

Cardiovascular diseases such as hypertension, coronary heart disease, and cerebrovascular disease are all metabolic-related diseases. It has been reported that metabolic syndrome can downregulate the key mediator of the host's innate immune response to pathogenesis, affecting the function of the innate and humoral immune systems [142]. Chronic low-grade inflammatory disease has been widely recognized as a feature of coronary heart disease, and its occurrence is closely related to inflammation [143]. The occurrence of hypertension is associated with oxidative stress, inflammation and the activation of the immune system [144]. IL-6, IL-1 and tumor necrosis factor α (TNF-α) levels are higher in patients with hypertension than in patients with normal blood pressure [145]. This may explain why patients with underlying cardiovascular disease found in the clinic are more susceptible to infection.

Kulcsar et al. showed that MERS-CoV infection can lead to prolonged respiratory tract inflammation, immune cell dysfunction, and changes in the expression profile of inflammatory mediators [146]. Lymphopenia and increased inflammatory mediators were found in SARS-CoV-2 infection [147]. Immune disorders caused by SARS-CoV

Table 3
Comparison of clinical data in and outside Wuhan.

	Wuhan				Outside Wuhan		
Hospital	Study 1 [9] Jin Yin-tan Hospital	Study 2 [11] Jin Yin-tan Hospital	Study 3 [139] Union hospital in Wuhan	Study 4 [10] Zhongnan Hospital of Wuhan University	Study 5 [134] Guangzhou Eighth People's Hospital	Study 6 [140] Hospitals in Hainan province	Study 7 [141] 10 designated hospitals in Shaanxi province
Study Duration	12/2019 – 2/1/2020	1/1 – 20/1/2020	16/1 – 29/1/2020	1/1 – 28/1/2020	10/1 – 24/2/2020	22/1 – 13/2/2020	23/1 – 7/3 – 2020
Case Numble	41	99	69	138	291	168	134
Any comorbidity	13 (32 %)	50 (51 %)	…	64 (46.4 %)	…	…	…
Diabetes	8 (20 %)	13 (13 %)	7 (10 %)	14 (10.1 %)	22 (7.6 %)	12 (7.1 %)	9 (6.7 %)
Hypertension	6 (15 %)	40 (40 %)	9 (13 %)	43 (31.2 %)	54 (18.5 %)	24 (14.3 %)	20 (14.9 %)
Cardiovascular disease	6 (15 %)		8 (12 %)	20 (14.5 %)	15 (5.1 %)	12 (7.1 %)	6 (4.5 %)
Chronic obstructive pulmonary disease	1 (2%)	1 (1 %)	4 (6 %)	4 (2.9 %)	…	10 (6%)	5 (3.7 %)
Malignancy	1 (2%)	1 (1 %)	4 (6 %)	10 (7.2 %)	…	2 (1.2 %)	5 (3.7 %)
Chronic liver disease	1 (2%)	11 (11 %)	1 (1%)	4 (2.9 %)	…	6 (3.6 %)	5 (3.7 %)
Complications							
Acute respiratory distress syndrome	12 (29 %)	17 (17 %)	…	27 (19.6 %)	…	17 (10.1 %)	3 (2.2 %)
Acute cardiac injury	5 (12 %)	…	…	10 (7.2 %)	15 (5.1 %)	4 (2.4 %)	…
Acute kidney injury	3 (7 %)	3 (3 %)	…	5 (3.6 %)	…	6 (3.6 %)	3 (2.2 %)
Secondary infection	4 (10 %)	5 (5%)	…	…	…	7 (4.2 %)	32 (23.9 %)
Shock	3 (7%)	4 (4%)	…	12 (8.7 %)	…	12 (7.1 %)	1 (0.7 %)
Prognosis							
Hospitalization	7 (17 %)	57 (58 %)	44 (65.7 %)	85 (61.6 %)	…	160 (95.2 %)	123 (91.8 %)
Discharge	28 (68 %)	31 (31 %)	18 (26.9 %)	47 (34.1 %)	…	6 (3.6 %)	9 (6.7 %)
Death	6 (15 %)	11 (11 %)	5 (7.5 %)	6 (4.3 %)	1 (0.3 %)	2 (1.2 %)	1 (0.7 %)

infection have also been reported [148]. These may lead to the exacerbation of the original cardiovascular disease, which is related to the death of some patients found in the clinic due to heart failure [88,103,132]. According to information released by the Shanghai Municipal Health and Family Planning Commission, the first COVID-19 death in Shanghai was in an individual who was 88 years old with a severe history of hypertension and cardiac insufficiency. An analysis of the cause of death suggested that the patient died of heart failure and systemic multiple organ dysfunction. Therefore, SARS-CoV-2 infection was just an inducement for exacerbations [124].

Overall, the heart and lungs are inseparable in the normal physiological functions of the human body. On the one hand, comorbidities and complications of the heart increase the risk of pneumonia infection and exacerbation; on the other hand, pneumonia infection may aggravate existing cardiovascular diseases, such as increased blood pressure, increased heart failure, and the recurrence of myocardial infarction.

6. Possible pathophysiology of CVD complications caused by coronavirus

6.1. Fever

Fever is a common symptom in patients with coronavirus infection [9,27,149]. Fever promotes the immune functions of humans and some animals and decreases the pathogenicity of some microbes. Antibody production, T-cell activation, neutrophil function, and macrophage oxidative metabolism have been reported to increase in the presence of fever [150–154]. However, to avoid excessively elevated body temperature affecting normal physiological functions, the body will activate sympathetic nerves and regulate circulatory function, which will increase the heart rate and cardiac output [155]. An increase in heart rate over a long period of time will lead to increased myocardial oxygen consumption and decreased cardiac output, which may cause ischemia or heart failure [156]. Many diseases with fever symptoms may be complicated by myocarditis, such as spotted fever rickettsioses infection [157], severe fever with thrombocytopenia syndrome [158], drug reaction with eosinophilia and systemic symptoms [159], dengue [160–162], complicated scrub typhus [163], herpes simplex virus infection [164], enteric fever [165].

A decrease in cardiac function may occur in febrile illnesses, but whether myocardial damage is due to fever or the underlying infection is not known [166]. Weissinger et al. found that in pigs with a bacterial infection with elevated body temperature, serum CK, lactate dehydrogenase (LD), and gamma-globulin (GG) levels were increased. The administration of antibiotics to these pigs and lowering their body temperature reduced CK and LD levels, but GG levels remained elevated, suggesting that the infection did not decrease. This study indicated that the levels of CK and LD were elevated due to fever caused by infection [167]. K L et al. discovered that a longer duration of fever was related to the occurrence of pericarditis after myocardial infarction [168]. Therefore, heart injury in coronavirus infection may be related to fever.

6.2. Hypoxemia

Severe pneumonia can cause significant gas exchange disturbances and lead to hypoxemia. Hypoxia reduces the energy production required for cell metabolism and increases the body's anaerobic digestion. Acidosis and oxygen free radicals accumulated in the cell destroy the phospholipid layer of the cell membrane. As hypoxia continues, the intracellular calcium ion concentration increases significantly, leading to a series of cell damage processes, including apoptosis [169]. At the same time, hypoxia can also induce inflammatory reactions, such as the infiltration of inflammatory cells and the release of cytokines, leading to further tissue ischemia, and may even cause myocardial infarction [13,170,171].

6.3. Inflammation

Previous lessons from coronavirus and influenza have shown that viral infections can cause acute coronary syndrome [172,173], arrhythmia [174], and exacerbation of heart failure [175], mainly due to a combination of significant systemic inflammation response and localized vascular inflammation at the arterial plaque, along with other effects [176–178]. Evidence has shown that SARS-CoV induces the expression of proinflammatory cytokines such as monocyte chemotactic protein 1 (MCP-1), transforming growth factor-beta 1 (TGF-beta1), TNF, IL-1 and IL-6 and interferon-β (IFN-β) in SARS patients and experimental animal models infected with SARS-CoV [179,180]. TNF and IL-1 family and IL-6 family cytokines are considered proinflammatory mediators of heart failure, and they have obvious negative inotropic effects, which may explain heart failure complications in SARS infection [181]. The acute heart injury might be due to the cytokine storm resulting from an overaggressive host immune response to SARS infection [30]. There is evidence indicating that myocardial inflammation induced by SARS-CoV is mainly mediated by macrophages and the resultant production of chemokines [95,96]. The nuclear factor-κB (NF-κB) signaling pathway associated with the induction of proinflammatory cytokines is activated in SARS-CoV-infected mice. Treatment with drugs that inhibited NF-κB activation led to a reduction in inflammation in both SARS-CoV-infected cultured cells and mice and significantly increased mouse survival after SARS-CoV infection, indicating that the activation of the NF-κB signaling pathway represents a major contribution to the inflammation induced after SARS-CoV infection and that NF-κB inhibitors are promising antivirals in infections caused by SARS-CoV and potentially other pathogenic human coronaviruses [182].

SARS-CoV-2 appears to affect themyocardium and cause myocarditis [128]. Myocardial injury is likely associated with infection-related myocarditis and/or ischemia [60]. Increases in inflammatory factors such as CRP, IL-1 and IL-6 were also discovered in SARS-CoV-2 infection [131,132,147]. Wu et al. believed that SARS-CoV-2 may cause heart damage by the cytokine storm [131]. Evidence has shown that SARS-CoV-2 may mainly affect T lymphocytes, especially CD4 + T cells, resulting in a significant decrease in lymphocyte numbers [183]. The extent of lymphopenia and an increase in inflammatory cytokines are related to the severity of the disease [147]. Critically ill COVID-19 patients had higher levels of IL6, IL10, TNFα, lactate dehydrogenase (LDH), and C-reactive protein than patients with mild COVID-19 [9,139,184], suggesting that inflammatory indicators are an important factor in the early diagnosis of severe COVID-19.

Most patients with coronavirus infection are in an inflammatory state, which places the patients in a hypercoagulable state. For example, COVID-19 leads to an increase in D-dimer levels in 40 % of patients, a decrease in activated partial thromboplastin time (APTT) in 16 % of patients, and a decrease in PT in 30 % of patients, further increasing the risk of embolism [11]. Hypercoagulability induced by inflammation might contribute to plaque rupture, with subsequent thrombosis and myocardial injury [185]. Therefore, clinicians should pay attention to COVID-19 patients with coronary heart disease to prevent myocardial injury and myocardial infarction.

6.4. Shock

Septic shock can be seen as a serious complication in SARS, MERS and COVID-19 [13,76,103]. Approximately 6.2 % of SARS-CoV-2 infections are complicated by shock [126]. It was reported that left ventricular dysfunction occurs in approximately 20 % of patients within 6 h after the onset of septic shock, and the incidence can increase to 60 % by 1–3 days after the onset of septic shock [186]. Myocardial dysfunction and cardiovascular inflammation might lead to elevated

creatine kinase and troponin [187], which might explain the high Hs-TnI in deceased patients.

6.5. Stress and anxiety

In addition to the abovementioned accompanying symptoms, anxiety and stress can also lead to adverse reactions such as accelerated heart rhythms and elevated blood pressure, especially in critically ill patients [188,189]. Health anxiety could be found in coronavirus-infected patients [190]. Generally, everyone experiences health anxiety to some degree, and the associated vigilance to a potential health-related threat can be protective. However, excessive health anxiety can be detrimental [190]. The literature indicates that stress can activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, leading to an increase in peripheral glucocorticoid and catecholamine levels [191]. High plasma catecholamine levels are associated with an increased risk of heart failure. Altered autonomic activity during depression can lead to arrhythmias. The activated SNS alters cardiac wall contractility and increases apoptotic pathways in cardiomyocytes, contributing to CVD development.

Although there is no relevant study on COVID-19 patients suffering from anxiety, medical workers have been reported to be anxious after direct contact with the patients [192,193]. A study by Sun et al. showed that some Chinese showed acute posttraumatic stress symptoms during the COVID-19 outbreak [194]. Therefore, psychological counseling should be conducted on patients in a timely manner, and anxiolytic drugs could be used when necessary.

6.6. Direct effect of coronavirus

As mentioned above, SARS-CoV was reported to lead to myocardial infection with a marked decrease in ACE2 expression, which may be responsible for myocardial dysfunction and adverse cardiac outcomes in patients with SARS [99]. Direct SARS-CoV infection of cardiomyocytes may also lead to myocarditis and impaired myocardial function. Coronavirus-induced myocarditis and its subsequent progression to dilated cardiomyopathy have been described in rabbit models [195]. SARS-CoV was found in heart samples from patients who died of SARS [76]. Pathological findings showed a marked increase in macrophage infiltration in patients with SARS-CoV in the heart, with evidence of myocardial damage. MERS-CoV was not detected in the heart tissue, and the heart showed no significant histological changes in MERS patients [111,112]. However, an animal model study clearly stated that MERS-CoV RNA could be seen in cardiac tissue, implying direct cardiac pathology [113]. Although myocarditis was reported in sporadic autopsy cases [128], there is still no clear pathological evidence supporting that SARS-CoV-2 can directly cause heart damage.

6.7. Complications of the drugs used in COVID-19 patients

The most frequently used drugs during hospitalization are glucocorticoids and antiviral drugs, as well as antibiotics. The secondary QT interval prolongation caused by the use of drugs during hospitalization cannot be ignored. Antiviral drugs (lopinavir, ritonavir), antibiotics (azithromycin, moxifloxacin, levofloxacin), antifungal drugs, glucocorticoids and some antiarrhythmic drugs, there is a potential risk of prolonging the QTc interval [196,197]. Drug-associated QT prolongation is associated with increased arrhythmic and non-arrhythmic mortality and it therefore continues to be an important metric of drug safety [198].

A small study in France enrolling 26 treated patients and 16 non-randomized controls showed that hydroxychloroquine alone or in combination with azithromycin shortened the time to resolution of viral shedding of COVID-19 [199]. Based on this study, clinicians in many countries have begun using these medications in clinical practice, and multiple randomized trials are being initiated. But there were occasional case reports of hydroxychloroquine prolonging the QT interval and provoking torsade de pointes when used to treat systemic lupus erythematosus [200–203]. The widely used antibiotic azithromycin was gradually recognized as a rare cause of prolonged QT, severe arrhythmia, and increased risk of sudden death [204–207]. Although there were no reports of arrhythmia death caused by the use of hydroxychloroquine, the use of hydroxychloroquine and azithromycin should also be noted [208].

7. Treatment related issues

Active support with expected management based on early prognostic indicators may improve recovery. Appropriate treatment of heart failure, arrhythmia, acute coronary syndrome and thrombosis are still important. With continued global cooperation on multiple methods, specific evidence-based treatment strategies for COVID-19 will emerge. In order to protect the wider population, antibody testing and effective vaccines will be needed to make a history of COVID-19. And some treatment related issues need attention.

Firstly, the use of ACEI / ARB drugs was controversial in the earlier phase of COVID-19 epidemic. But recently published studies suggested that there is no need for patients with hypertension to stop using ACEI / ARB or switch to other antihypertensive medicine [60,61,209]. Some conjectures [210] based on the disease mechanism in the early stage of the outbreak that ACEI / ARB may increase the infection of new coronavirus and the aggravation of COVID-19 by increasing the expression of ACE2 have been denied by more and more clinical evidence. We see that the continuous treatment of COVID-19 patients with hypertension with ACEI / ARB will not only cause the deterioration of the condition, but also continue to exert cardiovascular protection and even improve the prognosis [60,61,209].

Secondly, we should pay attention to the application of hydroxychloroquine [200–203] and azithromycin [204–207] for their side effects of prolonging the QT interval. Other drugs used to treat the COVID-19 patients, such as antiviral drugs (lopinavir, ritonavir), antibiotics (moxifloxacin, levofloxacin), antifungal drugs, glucocorticoids and some antiarrhythmic drugs, can cause the QT interval prolongation and should attract more attention. Reference by Sapp et al. would help to minimize risk of drug-induced ventricular arrhythmia during treatment of COVID-19 [211].

Thirdly, A recent study from JAMA reported that the mortality rate of patients with mechanical ventilation treatment was 88.1 % [212]. Multiple studies around the world have shown that the mortality rate of COVID-19 patients using ventilator was still high [213–215]. And it was believed that the ventilator should be used more cautiously in patients with COVID-19, which can reduce the mortality of patients using the ventilator by more than 50 % [216]. New guidelines should be established for when to use a ventilator for patients with COVID-19. We advocate the application of staged breathing support methods to delay the use of ventilator. Simple oxygen treatment like nasal oxygen supply may be safer and more effective.

Fourth, methylprednisolone are the classical immunosuppressive drugs, which are important to stop or delay the progress of the pneumonia, and have been proved to be effective for the treatment of acute respiratory distress syndrome (ARDS). In recent study [217], Wu at al. found that the administration of methylprednisolone appeared to reduce the risk of death in COVID-19 patients with ARDS. However, of those who received methylprednisolone treatment, 23 of 50 patients died. This is a rather high mortality of ~50 %. The indication, timing, dosage and duration, the application of methylprednisolone needs further investigation.

Fifth, the early report showed that remdesivir was highly effective in the control of SARS-CoV-2 infection in vitro [218]. But recent study published in Lancet showed that remdesivir did not reduce the mortality of COVID-19 patients [219]. However, another clinical trial showed that remdesivir accelerates recovery from advanced COVID-19

[220]. Another clinical trial showed that there was no significant difference in clinical outcome between the 5-day and 10-day course of remdesivir [221]. These data suggested remdesivir does not reduce the mortality of COVID-19 patients, but have an effect on shortening the course of disease in mild patients. And early medication may be better. The application of remdesivir needs further researches.

8. Conclusion

Clinical data indicate that comorbid cardiovascular disease will aggravate the severity of coronavirus infection, leading to a poor prognosis. Coronavirus may cause myocardial injury, and the prognosis of patients with complicated myocardial injury is poor. The mechanism of coronavirus causing myocardial injury and drug treatment options remain to be further studied.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work

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References

[1] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.

[2] L.L. Ren, Y.M. Wang, Z.Q. Wu, Z.C. Xiang, L. Guo, T. Xu, Y.Z. Jiang, Y. Xiong, Y.J. Li, X.W. Li, H. Li, G.H. Fan, X.Y. Gu, Y. Xiao, H. Gao, J.Y. Xu, F. Yang, X.M. Wang, C. Wu, L. Chen, Y.W. Liu, B. Liu, J. Yang, X.M.R. Wang, J. Dong, L. Li, C.L. Huang, J.P. Zhao, Y. Hu, Z.S. Cheng, L.L. Liu, Z.H. Qian, C. Qin, Q. Jin, B. Cao, J.W. Wang, Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chin. Med. J. (2020).

[3] V.J. Munster, M. Koopmans, N. van Doremalen, D. van Riel, E. de Wit, A novel coronavirus emerging in China - key questions for impact assessment, N. Engl. J. Med. 382 (8) (2020) 692–694.

[4] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, H.D. Chen, J. Chen, Y. Luo, H. Guo, R.D. Jiang, M.Q. Liu, Y. Chen, X.R. Shen, X.G. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F.X. Zhan, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature (2020).

[5] World Health Organization, Coronavirus Disease 2019 (COVID-19) Situation Report – 98, (2020) (Accessed April 27 2020), https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200427-sitrep-98-covid-19.pdf?sfvrsn=90323472_4.

[6] World Health Organization, Statement on the second meeting of the International Health Regulations, Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV), 2020, (2005) (Accessed 2020-01-30 2020), https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov).

[7] World Health Organization, WHO Characterizes COVID-19 As a Pandemic, (2020) (Accessed 2020-03-11 2020), https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen.

[8] CDC, The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China, Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi 41 (2) (2020) 145–151.

[9] C.L. Huang, Y.M. Wang, X.W. Li, L.L. Ren, J.P. Zhao, Y. Hu, L. Zhang, G.H. Fan, J.Y. Xu, X.Y. Gu, Z.S. Cheng, T. Yu, J.A. Xia, Y. Wei, W.J. Wu, X.L. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J.G. Xie, G.F. Wang, R.M. Jiang, Z.C. Gao, Q. Jin, J.W. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[10] Dawei Wang, Bo Hu, Chang Hu, Fangfang Zhu, Xing Liu, Jing Zhang, Binbin Wang, Hui Xiang, Zhenshun Cheng, Yong Xiong, Yan Zhao, Yirong Li, Xinghuan Wang, Zhiyong Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, Jama (2020).

[11] N.S. Chen, M. Zhou, X. Dong, J.M. Qu, F.Y. Gong, Y. Han, Y. Qiu, J.L. Wang, Y. Liu, Y. Wei, J.A. Xia, T. Yu, X.X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.

[12] Xiaobo Yang, Yuan Yu, Jiqian Xu, Huaqing Shu, Jia'an Xia, Hong Liu, Yongran Wu, Lu Zhang, Zhui Yu, Minghao Fang, Ting Yu, Yaxin Wang, Shangwen Pan, Xiaojing Zou, Shiying Yuan, You Shang, 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) S2213-2600(20)30079-5.

[13] Xun Li, Luwen Wang, Shaonan Yan, Fan Yang, Longkui Xiang, Jiling Zhu, Bo Shen, Zuojiong Gong, Clinical Characteristics of 25 Death Cases Infected With COVID-19 Pneumonia: a Retrospective Review of Medical Records in a Single Medical Center, medRxiv, Wuhan, China, 2020 2020.02.19.20025239.

[14] W.J. Guan, Z.Y. Ni, Y. Hu, W.H. Liang, C.Q. Ou, J.X. He, L. Liu, H. Shan, C.L. Lei, Du B. Hui DSC, L.J. Li, G. Zeng, K.Y. Yuen, R.C. Chen, C.L. Tang, T. Wang, P.Y. Chen, J. Xiang, S.Y. Li, J.L. Wang, Z.J. Liang, Y.X. Peng, L. Wei, Y. Liu, Y.H. Hu, P. Peng, J.L.M. Wang, J.Y. Liu, Z. Chen, G. Li, Z.J. Zheng, S.Q. Qiu, J. Luo, C.J. Ye, S.Y. Zhu, N.S. Zhong, Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. (2020).

[15] A.R. Fehr, S. Perlman, Coronaviruses: an overview of their replication and pathogenesis, Methods Mol. Biol. (Clifton, N.J.) 1282 (2015) 1–23.

[16] B.W. Neuman, B.D. Adair, C. Yoshioka, J.D. Quispe, G. Orca, P. Kuhn, R.A. Milligan, M. Yeager, M.J. Buchmeier, Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy, J. Virol. 80 (16) (2006) 7918–7928.

[17] M. Bárcena, G.T. Oostergetel, W. Bartelink, F.G. Faas, A. Verkleij, P.J. Rottier, A.J. Koster, B.J. Bosch, Cryo-electron tomography of mouse hepatitis virus: insights into the structure of the coronavirion, Proc. Natl. Acad. Sci. U. S. A. 106 (2) (2009) 582–587.

[18] Daniel Wrapp, Nianshuang Wang, Kizzmekia S. Corbett, Jory A. Goldsmith, Ching-Lin Hsieh, Olubukola Abiona, Barney S. Graham, Jason S. McLellan, Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation, bioRxiv, 2020 2020.02.11.944462.

[19] L.F.P. Ng, J.A. Hiscox, Coronaviruses in animals and humans, BMJ (Clin. Res. Ed.) 368 (2020) m634.

[20] D. Hamre, J.J. Procknow, A new virus isolated from the human respiratory tract, Proc. Soc. Exp. Biol. Med. 121 (1) (1966) 190–193.

[21] R.A. Fouchier, N.G. Hartwig, T.M. Bestebroer, B. Niemeyer, J.C. de Jong, J.H. Simon, A.D. Osterhaus, A previously undescribed coronavirus associated with respiratory disease in humans, Proc. Natl. Acad. Sci. U. S. A. 101 (16) (2004) 6212–6216.

[22] L. van der Hoek, K. Pyrc, M.F. Jebbink, W. Vermeulen-Oost, R.J. Berkhout, K.C. Wolthers, P.M. Wertheim-van Dillen, J. Kaandorp, J. Spaargaren, B. Berkhout, Identification of a new human coronavirus, Nat. Med. 10 (4) (2004) 368–373.

[23] R.A. Bucknall, A.R. Kalica, R.M. Chanock, Intracellular development and mechanism of hemadsorption of a human coronavirus, OC43, Proc. Soc. Exp. Biol. Med. 139 (3) (1972) 811–817.

[24] K. McIntosh, J.H. Dees, W.B. Becker, A.Z. Kapikian, R.M. Chanock, Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease, Proc. Natl. Acad. Sci. U. S. A. 57 (4) (1967) 933–940.

[25] D.A. Tyrrell, M.L. Bynoe, Cultivation of a novel type of common-cold virus in organ cultures, Br. Med. J. 1 (5448) (1965) 1467–1470.

[26] P.C. Woo, S.K. Lau, C.M. Chu, K.H. Chan, H.W. Tsoi, Y. Huang, B.H. Wong, R.W. Poon, J.J. Cai, W.K. Luk, L.L. Poon, S.S. Wong, Y. Guan, J.S. Peiris, K.Y. Yuen, Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia, J. Virol. 79 (2) (2005) 884–895.

[27] T.G. Ksiazek, D. Erdman, C.S. Goldsmith, S.R. Zaki, T. Peret, S. Emery, S. Tong, C. Urbani, J.A. Comer, W. Lim, P.E. Rollin, S.F. Dowell, A.E. Ling, C.D. Humphrey, W.J. Shieh, J. Guarner, C.D. Paddock, P. Rota, B. Fields, J. DeRisi, J.Y. Yang, N. Cox, J.M. Hughes, J.W. LeDuc, W.J. Bellini, L.J. Anderson, A novel coronavirus associated with severe acute respiratory syndrome, N. Engl. J. Med. 348 (20) (2003) 1953–1966.

[28] C. Drosten, S. Günther, W. Preiser, S. van der Werf, H.R. Brodt, S. Becker, H. Rabenau, M. Panning, L. Kolesnikova, R.A. Fouchier, A. Berger, A.M. Burguière, J. Cinatl, M. Eickmann, N. Escriou, K. Grywna, S. Kramme, J.C. Manuguerra, S. Müller, V. Rickerts, M. Stürmer, S. Vieth, H.D. Klenk, A.D. Osterhaus, H. Schmitz, H.W. Doerr, Identification of a novel coronavirus in patients with severe acute respiratory syndrome, N. Engl. J. Med. 348 (20) (2003) 1967–1976.

[29] A.M. Zaki, S. van Boheemen, T.M. Bestebroer, A.D. Osterhaus, R.A. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (19) (2012) 1814–1820.

[30] J.S. Peiris, S.T. Lai, L.L. Poon, Y. Guan, L.Y. Yam, W. Lim, J. Nicholls, W.K. Yee, W.W. Yan, M.T. Cheung, V.C. Cheng, K.H. Chan, D.N. Tsang, R.W. Yung, T.K. Ng, K.Y. Yuen, Coronavirus as a possible cause of severe acute respiratory syndrome, Lancet (London, England) 361 (9366) (2003) 1319–1325.

[31] J.F. Chan, S.K. Lau, K.K. To, V.C. Cheng, P.C. Woo, K.Y. Yuen, Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease, Clin. Microbiol. Rev. 28 (2) (2015) 465–522.

[32] T. Mizutani, A novel coronavirus, MERS-CoV, Uirusu 63 (1) (2013) 1–6.

[33] V.M. Corman, J. Lienau, M. Witzenrath, Coronaviruses as the cause of respiratory infections, Der Internist 60 (11) (2019) 1136–1145.

[34] S.A. Plotkin, The new coronavirus, the current king of China, J. Pediatric Infect. Dis. Soc. (2020).

[35] E.E. Walsh, J.H. Shin, A.R. Falsey, Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations, J. Infect. Dis. 208 (10) (2013) 1634–1642.

[36] J. Nokso-Koivisto, A. Pitkaranta, S. Blomqvist, T. Kilpi, T. Hovi, Respiratory coronavirus infections in children younger than two years of age, Pediatr. Infect. Dis. J. 19 (2) (2000) 164–166.

[37] L. Varghese, P. Zachariah, C. Vargas, P. LaRussa, R.T. Demmer, Y.E. Furuya, S. Whittier, C. Reed, M.S. Stockwell, L. Saiman, Epidemiology and clinical features of human coronaviruses in the pediatric population, J. Pediatr. Infect. Dis. Soc. 7 (2) (2018) 151–158.

[38] Salim Baharoon, Ziad A. Memish, MERS-CoV as an emerging respiratory illness: a review of prevention methods, Travel Med. Infect. Dis. (2019) 101520.

[39] E. de Wit, N. van Doremalen, D. Falzarano, V.J. Munster, SARS and MERS: recent insights into emerging coronaviruses, Nature reviews, Microbiology 14 (8) (2016) 523–534.

[40] Wei-jie Guan, Wen-hua Liang, Yi Zhao, Heng-rui Liang, Zi-sheng Chen, Yi-min Li, Xiao-qing Liu, Ru-chong Chen, Chun-li Tang, Tao Wang, Chun-quan Ou, Li. Li, Ping-yan Chen, Ling Sang, Wei Wang, Jian-fu Li, Cai-chen Li, Li-min Ou, Bo Cheng, Shan Xiong, Zheng-yi Ni, Jie Xiang Yu Hu, Lei Liu, Hong Shan, Chun-liang Lei, Yi-xiang Peng, Li Wei, Yong Liu, Ya-hua Hu, Peng. Peng, Jian-ming Wang, Ji-yang Liu, Zhong Chen, Gang Li, Zhi-jian Zheng, Shao-qin Qiu, Jie Luo, Chang-jiang Ye, Shao-yong Zhu, Lin-ling Cheng, Feng Ye, Shi-yue Li, Jin-ping Zheng, Nuo-fu Zhang, Nan-shan Zhong, Jian-xing He, Comorbidity and Its Impact on 1,590 Patients With COVID-19 in China: a Nationwide Analysis, medRxiv, 2020 2020.02.25.20027664.

[41] Berend Jan Bosch, Ruurd van der Zee, A.M. de Haan Cornelis, Peter J.M. Rottier, The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex, J. Virol. 77 (16) (2003) 8801–8811.

[42] F. Li, Structure, Function, and Evolution of Coronavirus Spike Proteins, Annu. Rev. Virol. 3 (1) (2016) 237–261.

[43] Wenhui Li, Michael J. Moore, Natalya Vasilieva, Jianhua Sui, Swee Kee Wong, Michael A. Berne, Mohan Somasundaran, John L. Sullivan, Katherine Luzuriaga, Thomas C. Greenough, Hyeryun Choe, Michael Farzan, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 426 (6965) (2003) 450–454.

[44] Heike Hofmann, Krzysztof Pyrc, Liavander Hoek, Martina Geier, Ben Berkhout, Stefan Pohlmann, Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry, Proc. Natl. Acad. Sci. U. S. A. 102 (22) (2005) 7988–7993.

[45] V. Stalin Raj, Huihui Mou, Saskia L. Smits, Dick H.W. Dekkers, Marcel A. Muller, Ronald Dijkman, Doreen Muth, Jeroen A.A. Demmers, Ali Zaki, Ron A.M. Fouchier, Volker Thiel, Christian Drosten, Peter J.M. Rottier, Albert D.M.E. Osterhaus, Berend Jan Bosch, Bart L. Haagmans, Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, Nature 495 (7440) (2013) 251–254.

[46] C.L. Yeager, R.A. Ashmun, R.K. Williams, C.B. Cardellichio, L.H. Shapiro, A.T. Look, K.V. Holmes, Human aminopeptidase N is a receptor for human coronavirus 229E, Nature 357 (6377) (1992) 420–422.

[47] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A.S. Slutsky, D. Liu, C. Qin, C. Jiang, J.M. Penninger, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (8) (2005) 875–879.

[48] Yu Zhao, Zixian Zhao, Yujia Wang, Yueqing Zhou, Ma Yu, Zuo Wei, Single-cell RNA Expression Profiling of ACE2, the Putative Receptor of Wuhan 2019-nCov, bioRxiv, 2020 2020.01.26.919985.

[49] M.A. Crackower, R. Sarao, G.Y. Oudit, C. Yagil, I. Kozieradzki, S.E. Scanga, A.J. Oliveira-dos-Santos, J. da Costa, L. Zhang, Y. Pei, J. Scholey, C.M. Ferrario, A.S. Manoukian, M.C. Chappell, P.H. Backx, Y. Yagil, J.M. Penninger, Angiotensin-converting enzyme 2 is an essential regulator of heart function, Nature 417 (6891) (2002) 822–828.

[50] V.B. Patel, J.C. Zhong, M.B. Grant, G.Y. Oudit, Role of the ACE2/Angiotensin 1-7 Axis of the renin-angiotensin system in heart failure, Circ. Res. 118 (8) (2016) 1313–1326.

[51] S.R. Tipnis, N.M. Hooper, R. Hyde, E. Karran, G. Christie, A.J. Turner, A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase, J. Biol. Chem. 275 (43) (2000) 33238–33243.

[52] I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2) (2004) 631–637.

[53] P.E. Gallagher, C.M. Ferrario, E.A. Tallant, Regulation of ACE2 in cardiac myocytes and fibroblasts, American journal of physiology, Heart Circulatory Physiol. 295 (6) (2008) H2373–9.

[54] K. Kuba, Y. Imai, S. Rao, C. Jiang, J.M. Penninger, Lessons from SARS: control of acute lung failure by the SARS receptor ACE2, J. Mol. Med. (Berlin, Germany) 84 (10) (2006) 814–820.

[55] P.P. Liu, A. Blet, D. Smyth, H. Li, The science underlying COVID-19: implications for the cardiovascular system, Circulation (2020).

[56] R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou, Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2, Science (New York, N.Y.) (2020).

[57] G.E. Callera, T.T. Antunes, J.W. Correa, D. Moorman, A. Gutsol, Y. He, A.N. Cat, A.M. Briones, A.C. Montezano, K.D. Burns, R.M. Touyz, Differential renal effects of candesartan at high and ultra-high doses in diabetic mice-potential role of the ACE2/AT2R/Mas axis, Biosci. Rep. 36 (5) (2016).

[58] C.M. Ferrario, J. Jessup, M.C. Chappell, D.B. Averill, K.B. Brosnihan, E.A. Tallant, D.I. Diz, P.E. Gallagher, Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2, Circulation 111 (20) (2005) 2605–2610.

[59] Y. Liu, Y. Yang, C. Zhang, F. Huang, F. Wang, J. Yuan, Z. Wang, J. Li, J. Li, C. Feng, Z. Zhang, L. Wang, L. Peng, L. Chen, Y. Qin, D. Zhao, S. Tan, L. Yin, J. Xu, C. Zhou, C. Jiang, L. Liu, Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Science China, Life Sci. 63 (3) (2020) 364–374.

[60] Tao Guo, Yongzhen Fan, Ming Chen, Xiaoyan Wu, Lin Zhang, Tao He, Hairong Wang, Jing Wan, Xinghuan Wang, Zhibing Lu, Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19), JAMA Cardiol. (2020).

[61] Peng Zhang, Li Hua Zhu, Jingjing Cai, Fang Lei, Juan-Juan Qin, Jing Xie, Ye-Mao Liu, Yan-Ci Zhao, Xuewei Huang, Lijin Lin, Meng Xia, Ming-Ming Chen, Xu Cheng, Xiao Zhang, Deliang Guo, Yuanyuan Peng, Yan-Xiao Ji, Jing Chen, Zhi-Gang She, Yibin Wang, Xu Qingbo, Renfu Tan, Haitao Wang, Jun Lin, Pengcheng Luo, Fu Shouzhi, Hongbin Cai, Ping Ye, Bing Xiao, Weiming Mao, Liming Liu, Youqin Yan, Mingyu Liu, Manhua Chen, Xiao-Jing Zhang, Xinghuan Wang, Rhian M. Touyz, Jiahong Xia, Bing-Hong Zhang, Xiaodong Huang, Yufeng Yuan, Loomba Rohit, Peter P. Liu, Hongliang Li, Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19, Circ. Res. (2020).

[62] K. McIntosh, E.F. Ellis, L.S. Hoffman, T.G. Lybass, J.J. Eller, V.A. Fulginiti, The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children, J. Pediatr. 82 (4) (1973) 578–590.

[63] Judith M. Graat, Evert G. Schouten, Marie-Louise A. Heijnen, Frans J. Kok, Esther G.M. Pallast, Sabine C. de Greeff, J. Wendelien Dorigo-Zetsma, A prospective, community-based study on virologic assessment among elderly people with and without symptoms of acute respiratory infection, J. Clin. Epidemiol. 56 (12) (2003) 1218–1223.

[64] Frederic Pene, Annabelle Merlat, Astrid Vabret, Flore Rozenberg, Agnes Buzyn, Francois Dreyfus, Alain Cariou, Francois Freymuth, Pierre Lebon, Coronavirus 229E-related pneumonia in immunocompromised patients, Clin. Infect. Dis. 37 (7) (2003) 929–932.

[65] Jay B. Varkey, Basil Varkey, Viral infections in patients with chronic obstructive pulmonary disease, Curr. Opin. Pulm. Med. 14 (2) (2008) 89–94.

[66] Geoffrey J. Gorse, Theresa Z. O'Connor, Susan L. Hall, Joseph N. Vitale, Kristin L. Nichol, Human coronavirus and acute respiratory illness in older adults with chronic obstructive pulmonary disease, J. Infect. Dis. 199 (6) (2009) 847–857.

[67] Liavander Hoek, Human coronaviruses: what do they cause? Antivir. Ther. 12 (4) (2007) 651–658.

[68] Stanley Perlman, Jason Netland, Coronaviruses post-SARS: update on replication and pathogenesis, Nat. Rev. Microbiol. 7 (6) (2009) 439–450.

[69] T.K. Cabeça, C. Granato, N. Bellei, Epidemiological and clinical features of human coronavirus infections among different subsets of patients, Influenza Other Respir. Viruses 7 (6) (2013) 1040–1047.

[70] J. Lee, G.A. Storch, Characterization of human coronavirus OC43 and human coronavirus NL63 infections among hospitalized children < 5 years of age, Pediatr. Infect. Dis. J. 33 (8) (2014) 814–820.

[71] G.B. Kim, S. Park, B.S. Kwon, J.W. Han, Y.W. Park, Y.M. Hong, Evaluation of the temporal association between kawasaki disease and viral infections in South Korea, Korean Circ. J. 44 (4) (2014) 250–254.

[72] K. Shirato, Y. Imada, M. Kawase, K. Nakagaki, S. Matsuyama, F. Taguchi, Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease, J. Med. Virol. 86 (12) (2014) 2146–2153.

[73] WHO, D.O.C.D.S.A. RESPONSE (Ed.), Consensus Document on the Epidemiology of Severe Acute Respiratory Syndrome (SARS), 2003.

[74] W.C. Cao, S.J. de Vlas, J.H. Richardus, The severe acute respiratory syndrome epidemic in mainland China dissected, Infect. Dis. Rep. 3 (1) (2011) e2.

[75] Q. Chen, W.N. Liang, G.F. Liu, M. Liu, X.Q. Xie, J. Wu, X. He, Z.J. Liu, Case fatality rate of severe acute respiratory syndromes in Beijing, Biomed. Environ. Sci. 18 (4) (2005) 220–226.

[76] G.A. Farcas, S.M. Poutanen, T. Mazzulli, B.M. Willey, J. Butany, S.L. Asa, P. Faure, P. Akhavan, D.E. Low, K.C. Kain, Fatal severe acute respiratory syndrome is associated with multiorgan involvement by coronavirus, J. Infect. Dis. 191 (2) (2005) 193–197.

[77] E.H. Lau, C.A. Hsiung, B.J. Cowling, C.H. Chen, L.M. Ho, T. Tsang, C.W. Chang, C.A. Donnelly, G.M. Leung, A comparative epidemiologic analysis of SARS in Hong Kong, Beijing and Taiwan, BMC Infect. Dis. 10 (2010) 50.

[78] Gabriel M. Leung, Anthony J. Hedley, Lai-Ming Ho, Patsy Chau, Irene O.L. Wong, Thuan Q. Thach, Azra C. Ghani, Christl A. Donnelly, Christophe Fraser, Steven Riley, Neil M. Ferguson, Roy M. Anderson, Thomas Tsang, Pak-Yin Leung, Vivian Wong, Jane C.K. Chan, Eva Tsui, Su-Vui Lo, Tai-Hing Lam, The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients, Ann. Intern. Med. 141 (9) (2004) 662–673.

[79] N. Jia, D. Feng, L.Q. Fang, J.H. Richardus, X.N. Han, W.C. Cao, S.J. de Vlas, Case fatality of SARS in mainland China and associated risk factors, Trop. Med. Int. Health: TM & IH (2009) 21–27.

[80] A.C. Ghani, C.A. Donnelly, D.R. Cox, J.T. Griffin, C. Fraser, T.H. Lam, L.M. Ho, W.S. Chan, R.M. Anderson, A.J. Hedley, G.M. Leung, Methods for estimating the case fatality ratio for a novel, emerging infectious disease, Am. J. Epidemiol. 162 (5) (2005) 479–486.

[81] J.S.M. Peiris, C.M. Chu, V.C.C. Cheng, K.S. Chan, I.F.N. Hung, L.L.M. Poon, K.I. Law, B.S.F. Tang, T.Y.W. Hon, C.S. Chan, K.H. Chan, J.S.C. Ng, B.J. Zheng,

W.L. Ng, R.W.M. Lai, Y. Guan, K.Y. Yuen, Hku Uch Sars Study Group, Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study, Lancet (London, England) 361 (9371) (2003) 1767–1772.
[82] Kow-Tong Chen, Shiing-Jer Twu, Hsiao-Ling Chang, Wu Yi-Chun, Chu-Tzu Chen, Ting-Hsiang Lin, Sonja J. Olsen, Scott F. Dowell, Su Ih-Jen, Sars response team taiwan, SARS in Taiwan: an overview and lessons learned, Int. J. Infect. Dis. 9 (2) (2005) 77–85.
[83] Benjamin J. Cowling, Matthew P. Muller, Irene O.L. Wong, Lai-Ming Ho, Su-Vui Lo, Thomas Tsang, Tai Hing Lam, Marie Louie, Gabriel M. Leung, Clinical prognostic rules for severe acute respiratory syndrome in low- and high-resource settings, Arch. Intern. Med. 166 (14) (2006) 1505–1511.
[84] ChristopherM. Booth, LarissaM. Matukas, George A. Tomlinson, Anita R. Rachlis, David B. Rose, Hy A. Dwosh, SharonL. Walmsley, Tony Mazzulli, Monica Avendano, Peter Derkach, Issa E. Ephtimios, Ian Kitai, Barbara D. Mederski, Steven B. Shadowitz, Wayne L. Gold, Laura A. Hawryluck, Elizabeth Rea, Jordan S. Chenkin, David W. Cescon, Susan M. Poutanen, Allan S. Detsky, Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area, Jama 289 (21) (2003) 2801–2809.
[85] Nelson Lee, David Hui, Wu Alan, Paul Chan, Peter Cameron, Gavin M. Joynt, Anil Ahuja, Man Yee Yung, C.B. Leung, K.F. To, S.F. Lui, C.C. Szeto, Sydney Chung, Joseph J.Y. Sung, A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (20) (2003) 1986–1994.
[86] J.W. Chan, C.K. Ng, Y.H. Chan, T.Y. Mok, S. Lee, S.Y. Chu, W.L. Law, M.P. Lee, P.C. Li, Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS), Thorax 58 (8) (2003) 686–689.
[87] Kenneth W. Tsang, Pak L. Ho, Gaik C. Ooi, Wilson K. Yee, Teresa Wang, Moira Chan-Yeung, Wah K. Lam, Wing H. Seto, Loretta Y. Yam, Thomas M. Cheung, Poon C. Wong, Bing Lam, Mary S. Ip, Jane Chan, Kwok Y. Yuen, Kar N. Lai, A cluster of cases of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (20) (2003) 1977–1985.
[88] W.W. Wong, T.L. Chen, S.P. Yang, F.D. Wang, N.C. Cheng, B.I. Kuo, Tsai C.A. Yu KW, Y.S. Lin, I.R. Lee, C.Y. Chi, C.J. Lai, C.J.H. Lai, H.P. Chen, C.Y. Liu, Clinical characteristics of fatal patients with severe acute respiratory syndrome in a medical center in Taipei, J. Chin. Med. Assoc. 66 (6) (2003) 323–327.
[89] C.Y. Chen, C.H. Lee, C.Y. Liu, J.H. Wang, L.M. Wang, R.P. Perng, Clinical features and outcomes of severe acute respiratory syndrome and predictive factors for acute respiratory distress syndrome, J. Chin. Med. Assoc. 68 (1) (2005) 4–10.
[90] S.S. Hu, Y.J. Yang, M.L. Zhu, Z. Chen, Z.P. Zou, J.G. He, Y.F. Wu, D.M. Han, Effects of underlying cerebrocardiovascular diseases on the incidence of critical conditions and multiple organs dysfunction syndrome in severe acute respiratory syndrome cases, Zhonghua Yi Xue Za Zhi 84 (15) (2004) 1257–1259.
[91] S.S. Li, C.W. Cheng, C.L. Fu, Y.H. Chan, M.P. Lee, J.W. Chan, S.F. Yiu, Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study, Circulation 108 (15) (2003) 1798–1803.
[92] C.M. Yu, R.S. Wong, E.B. Wu, S.L. Kong, J. Wong, G.W. Yip, Y.O. Soo, M.L. Chiu, Y.S. Chan, D. Hui, N. Lee, A. Wu, C.B. Leung, J.J. Sung, Cardiovascular complications of severe acute respiratory syndrome, Postgrad. Med. J. 82 (964) (2006) 140–144.
[93] Joseph S.M. Peiris, Kwok Y. Yuen, Albert D.M.E. Osterhaus, Klaus Stöhr, The severe acute respiratory syndrome, N. Engl. J. Med. 349 (25) (2003) 2431–2441.
[94] Y. Yin, R.G. Wunderink, MERS, SARS and other coronaviruses as causes of pneumonia, Respirology (Carlton, Vic.) 23 (2) (2018) 130–137.
[95] D.M. Hwang, D.W. Chamberlain, S.M. Poutanen, D.E. Low, S.L. Asa, J. Butany, Pulmonary pathology of severe acute respiratory syndrome in Toronto, Mod. Pathol. 18 (1) (2005) 1–10.
[96] M.J. Cameron, L. Ran, L. Xu, A. Danesh, J.F. Bermejo-Martin, C.M. Cameron, M.P. Muller, W.L. Gold, S.E. Richardson, S.M. Poutanen, B.M. Willey, M.E. DeVries, Y. Fang, C. Seneviratne, S.E. Bosinger, D. Persad, P. Wilkinson, L.D. Greller, R. Somogyi, A. Humar, S. Keshavjee, M. Louie, M.B. Loeb, J. Brunton, A.J. McGeer, D.J. Kelvin, Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome, J. Virol. 81 (16) (2007) 8692–8706.
[97] S. Haga, N. Yamamoto, C. Nakai-Murakami, Y. Osawa, K. Tokunaga, T. Sata, N. Yamamoto, T. Sasazuki, Y. Ishizaka, Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry, Proc. Natl. Acad. Sci. U. S. A. 105 (22) (2008) 7809–7814.
[98] M.J. Cameron, J.F. Bermejo-Martin, A. Danesh, M.P. Muller, D.J. Kelvin, Human immunopathogenesis of severe acute respiratory syndrome (SARS), Virus Res. 133 (1) (2008) 13–19.
[99] G.Y. Oudit, Z. Kassiri, C. Jiang, P.P. Liu, S.M. Poutanen, J.M. Penninger, J. Butany, SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS, Eur. J. Clin. Invest. 39 (7) (2009) 618–625.
[100] Tariq Alhogbani, Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus, Ann. Saudi Med. 36 (1) (2016) 78–80.
[101] Abdullah Assiri, Allison McGeer, Trish M. Perl, Connie S. Price, Abdullah A. Al Rabeeah, Derek A.T. Cummings, Zaki N. Alabdullatif, Maher Assad, Abdulmohsen Almulhim, Hatem Makhdoom, Hossam Madani, Rafat Alhakeem, Jaffar A. Al-Tawfiq, Matthew Cotten, Simon J. Watson, Paul Kellam, Alimuddin I. Zumla, Ziad A. Memish, Ksa Mers- CoV Investigation Team, Hospital outbreak of Middle East respiratory syndrome coronavirus, N. Engl. J. Med. 369 (5) (2013) 407–416.
[102] Ziad A. Memish, Alimuddin I. Zumla, Abdullah Assiri, Middle East respiratory syndrome coronavirus infections in health care workers, N. Engl. J. Med. 369 (9) (2013) 884–886.
[103] Yaseen M. Arabi, Ahmed A. Arifi, Hanan H. Balkhy, Hani Najm, Abdulaziz S. Aldawood, Alaa Ghabashi, Hassan Hawa, Adel Alothman, Abdulaziz Khaldi, Basel Al Raiy, Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection, Ann. Intern. Med. 160 (6) (2014) 389–397.
[104] Ziad A. Memish, Matthew Cotten, Simon J. Watson, Paul Kellam, Alimuddin Zumla, Rafat F. Alhakeem, Abdullah Assiri, AbdullahA. Al Rabeeah, Jaffar A. Al-Tawfiq, Community case clusters of Middle East respiratory syndrome coronavirus in Hafr Al-Batin, Kingdom of Saudi Arabia: a descriptive genomic study, Int. J. Infect. Dis. 23 (2014) 63–68.
[105] Abdullah Assiri, Jaffar A. Al-Tawfiq, Abdullah A. Al-Rabeeah, Fahad A. Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flemban, Wafa N. Al-Nassir, Hanan H. Balkhy, Rafat F. Al-Hakeem, Hatem Q. Makhdoom, Alimuddin I. Zumla, Ziad A. Memish, Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study, Lancet Infect. Dis. 13 (9) (2013) 752–761.
[106] Jaffar A. Al-Tawfiq, Kareem Hinedi, Jihad Ghandour, Hanan Khairalla, Samir Musleh, Alaa Ujayli, Ziad A. Memish, Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients, Clin. Infect. Dis. 59 (2) (2014) 160–165.
[107] A. Badawi, S.G. Ryoo, Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis, Int. J. Infect. Dis. 49 (2016) 129–133.
[108] M.A. Garout, H.A.A. Jokhdar, H.A. Aljandali, A.R. Zein, R.A. Goweda, A. Hassan-Hussein, Mortality rate of ICU patients with the Middle East respiratory syndrome - coronavirus infection at King Fahad Hospital, Jeddah, Saudi Arabia, Cent. Eur. J. Public Health 26 (2) (2018) 87–91.
[109] Gouri Rani Banik, Amani Salem Alqahtani, Robert Booy, Harunor Rashid, Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia, Virol. Sin. 31 (1) (2016) 81–84.
[110] T. Alhogbani, Acute myocarditis associated with novel Middle east respiratory syndrome coronavirus, Ann. Saudi Med. 36 (1) (2016) 78–80.
[111] K.O. Alsaad, A.H. Hajeer, M. Al Balwi, M. Al Moaiqel, N. Al Oudah, A. Al Ajlan, S. AlJohani, S. Alsolamy, G.E. Gmati, H. Balkhy, H.H. Al-Jahdali, S.A. Baharoon, Y.M. Arabi, Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study, Histopathology 72 (3) (2018) 516–524.
[112] D.L. Ng, F. Al Hosani, M.K. Keating, S.I. Gerber, T.L. Jones, M.G. Metcalfe, S. Tong, Y. Tao, N.N. Alami, L.M. Haynes, M.A. Mutei, L. Abdel-Wareth, T.M. Uyeki, D.L. Swerdlow, M. Barakat, S.R. Zaki, Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014, Am. J. Pathol. 186 (3) (2016) 652–658.
[113] A.S. Agrawal, T. Garron, X. Tao, B.H. Peng, M. Wakamiya, T.S. Chan, R.B. Couch, C.T. Tseng, Generation of a transgenic mouse model of Middle East respiratory syndrome coronavirus infection and disease, J. Virol. 89 (7) (2015) 3659–3670.
[114] W.J. Tan, X. hao, X.J. Ma, A novel coronavirus genome identified in a cluster of pneumonia cases-Wuhan, China 2019–2020, China CDC Weekly 2 (2020) (2020) 61–62.
[115] C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao, A novel coronavirus outbreak of global health concern, Lancet 395 (10223) (2020) 470–473.
[116] C.I. Paules, H.D. Marston, A.S. Fauci, Coronavirus infections-more than just the common cold, JAMA (2020).
[117] J.F.W. Chan, S.F. Yuan, K.H. Kok, K.K.W. To, H. Chu, J. Yang, F.F. Xing, J.L. Liu, C.C.Y. Yip, R.W.S. Poon, H.W. Tsoi, S.K.F. Lo, K.H. Chan, V.K.M. Poon, W.M. Chan, J.D. Ip, J.P. Cai, V.C.C. Cheng, H.L. Chen, C.K.M. Hui, K.Y. Yuen, A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 395 (10223) (2020) 514–523.
[118] World Health Organization, Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), (2020) (Accessed March 19 2020), https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.
[119] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Li, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam, J.T.K. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. (2020).
[120] W. Wang, J. Tang, F. Wei, Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol. 92 (4) (2020) 441–447.
[121] W.G. Carlos, C.S. Dela Cruz, B. Cao, S. Pasnick, S. Jamil, Novel Wuhan (2019-nCoV) coronavirus, Am. J. Respir. Crit. Care Med. 201 (4) (2020) P7–P8.
[122] L.T. Phan, T.V. Nguyen, Q.C. Luong, T.V. Nguyen, H.T. Nguyen, H.Q. Le, T.V. Nguyen, T.M. Cao, Q.D. Pham, Importation and human-to-Human transmission of a novel coronavirus in vietnam, N. Engl. J. Med. 382 (9) (2020) 872–874.
[123] K. Liu, Y.Y. Fang, Y. Deng, W. Liu, M.F. Wang, J.P. Ma, W. Xiao, Y.N. Wang, M.H. Zhong, C.H. Li, G.C. Li, H.G. Liu, Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province, Chin. Med. J. (2020).
[124] B. Li, J. Yang, F. Zhao, L. Zhi, X. Wang, L. Liu, Z. Bi, Y. Zhao, Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China, Clin. Res. Cardiol. (2020).
[125] Xu Huayan, Keke Hou, Xu Hong, Zhenlin Li, Huizhu Chen, Zhang Na, Xu Rong, Fu Hang, Ran Sun, Lingyi Wen, Linjun Xie, Hui Liu, Kun Zhang, Joseph B. Selvanayagam, Fu Chuan, Shihua Zhao, Zhigang Yang, Ming Yang,

Yingkun Guo, Acute Myocardial Injury of Patients With Coronavirus Disease 2019, medRxiv, 2020 2020.03.05.20031591.
[126] A.J. Rodriguez-Morales, J.A. Cardona-Ospina, E. Gutiérrez-Ocampo, R. Villamizar-Peña, Y. Holguin-Rivera, J.P. Escalera-Antezana, L.E. Alvarado-Arnez, D.K. Bonilla-Aldana, C. Franco-Paredes, A.F. Henao-Martinez, A. Paniz-Mondolfi, G.J. Lagos-Grisales, E. Ramírez-Vallejo, J.A. Suárez, L.I. Zambrano, W.E. Villamil-Gómez, G.J. Balbin-Ramon, A.A. Rabaan, H. Harapan, K. Dhama, H. Nishiura, H. Kataoka, T. Ahmad, R. Sah, Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis, Travel Med. Infect. Dis. (2020) 101623.
[127] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan, Y. Shang, 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).
[128] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (4) (2020) 420–422.
[129] Riccardo M. Inciardi, Laura Lupi, Gregorio Zaccone, Leonardo Italia, Michela Raffo, Daniela Tomasoni, Dario S. Cani, Manuel Cerini, Davide Farina, Emanuele Gavazzi, Roberto Maroldi, Marianna Adamo, Enrico Ammirati, Gianfranco Sinagra, Carlo M. Lombardi, Marco Metra, Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19), JAMA Cardiol. (2020).
[130] Hongde Hu, Fenglian Ma, Xin Wei, Yuan Fang, Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin, Eur. Heart J. (2020).
[131] Chaomin Wu, Xianglin Hu, Jianxin Song, Chunling Du, Jie Xu, Dong Yang, Dechang Chen, Ming Zhong, Jinjun Jiang, Weining Xiong, Ke Lang, Yuye Zhang, Guohua Shi, Lei Xu, Yuanlin Song, Xin Zhou, Ming Wei, Junhua Zheng, Heart Injury Signs Are Associated With Higher and Earlier Mortality in Coronavirus Disease 2019 (COVID-19), medRxiv, 2020 2020.02.26.20028589.
[132] Bicheng Zhang, Xiaoyang Zhou, Yanru Qiu, Fan Feng, Jia Feng, Yifan Jia, Hengcheng Zhu, Ke Hu, Jiasheng Liu, Zaiming Liu, Shihong Wang, Yiping Gong, Chenliang Zhou, Ting Zhu, Yanxiang Cheng, Zhichao Liu, Hongping Deng, Fenghua Tao, Yijun Ren, Biheng Cheng, Ling Gao, Xiongfei Wu, Lilei Yu, Zhixin Huang, Zhangfan Mao, Qibin Song, Bo Zhu, Jun Wang, Clinical Characteristics of 82 Death Cases With COVID-19, medRxiv, 2020 2020.02.26.20028191.
[133] G. Lippi, M. Plebani, Laboratory abnormalities in patients with COVID-2019 infection, Clin. Chem. Lab. Med. (2020).
[134] youbin liu, Jinglong Li, Dehui liu, Huafeng Song, Chunlin chen, Mingfang lv, Xing pei, Hu Zhongwei, Clinical Features and Outcomes of 2019 Novel Coronavirus-infected Patients With Cardiac Injury, medRxiv, 2020 2020.03.11.20030957.
[135] Lei Gao, Dan Jiang, Xuesong Wen, Xiaocheng Cheng, Min Sun, Bin He, Lin-na You, Peng Lei, Xiao-wei Tan, Shu Qin, Guoqiang Cai, Dongying Zhang, Prognostic Value of NT-proBNP in Patients With Severe COVID-19, medRxiv, 2020 2020.03.07.20031575.
[136] Shaobo Shi, Mu Qin, Bo Shen, Yuli Cai, Tao Liu, Fan Yang, Wei Gong, Xu Liu, Jinjun Liang, Qinyan Zhao, He Huang, Bo Yang, Congxin Huang, Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China, JAMA Cardiol. (2020).
[137] Ivair JoséMorais Júnior, Richard Costa Polveiro, Gabriel Medeiros Souza, Daniel Inserra Bortolin, Flávio Tetsuo Sassaki, Alison Talis Martins Lima, The Global Population of SARS-CoV-2 Is Composed of Six Major Subtypes, bioRxiv, 2020 2020.04.14.040782.
[138] Xiaolu Tang, Changcheng Wu, Xiang Li, Yuhe Song, Xinmin Yao, Xinkai Wu, Yuange Duan, Hong Zhang, Yirong Wang, Zhaohui Qian, Jie Cui, Jian Lu, On the origin and continuing evolution of SARS-CoV-2, Sci. Rev. (2020).
[139] Z. Wang, B. Yang, Q. Li, L. Wen, R. Zhang, Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China, Clin. Infect. Dis. (2020).
[140] Shijiao Yan, Xingyue Song, Feng Lin, Haiyan Zhu, Xiaozhi Wang, Min Li, Jianwen Ruan, Changfeng Lin, Xiaoran Liu, Qiang Wu, Zhiqian Luo, Wenning Fu, Song Chen, Yong Yuan, Shengxing Liu, Jinjian Yao, Chuanzhu Lv, Clinical Characteristics of Coronavirus Disease 2019 in Hainan, China, medRxiv, 2020 2020.03.19.20038539.
[141] Puyu Shi, Guoxia Ren, Jun Yang, Zhiqiang Li, Shujiao Deng, Miao Li, Shasha Wang, Xiaofeng Xu, Fuping Chen, Yuanjun Li, Chunyan Li, Xiaohua Yang, Zhaofeng Xie, Zhengxia Wu, Mingwei Chen, Clinical Characteristics of Imported and Second-generation COVID-19 Cases Outside Wuhan, China: a Multicenter Retrospective Study, medRxiv, 2020 2020.04.19.20071472.
[142] J.I. Odegaard, A. Chawla, Connecting type 1 and type 2 diabetes through innate immunity, Cold Spring Harb. Perspect. Med. 2 (3) (2012) a007724.
[143] E. Golia, G. Limongelli, F. Natale, F. Fimiani, V. Maddaloni, I. Pariggiano, R. Bianchi, M. Crisci, L. D'Acierno, R. Giordano, G. Di Palma, M. Conte, P. Golino, M.G. Russo, R. Calabrò, P. Calabrò, Inflammation and cardiovascular disease: from pathogenesis to therapeutic target, Curr. Atheroscler. Rep. 16 (9) (2014) 435.
[144] A. Agita, M.T. Alsagaff, Inflammation, immunity, and hypertension, Acta Med. Indones. 49 (2) (2017) 158–165.
[145] Q.N. Dinh, G.R. Drummond, C.G. Sobey, S. Chrissobolis, Roles of inflammation, oxidative stress, and vascular dysfunction in hypertension, Biomed Res. Int. 2014 (2014) 406960.
[146] K.A. Kulcsar, C.M. Coleman, S.E. Beck, M.B. Frieman, Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection, JCI Insight 4 (20) (2019).
[147] Jing Liu, Sumeng Li, Jia Liu, Boyun Liang, Xiaobei Wang, Hua Wang, Wei Li, Qiaoxia Tong, Jianhua Yi, Lei Zhao, Lijuan Xiong, Chunxia Guo, Jin Tian, Jinzhuo Luo, Jinghong Yao, Ran Pang, Hui Shen, Cheng Peng, Ting Liu, Qian Zhang, Jun Wu, Ling Xu, Sihong Lu, Baoju Wang, Zhihong Weng, Chunrong Han, Huabing Zhu, Ruxia Zhou, Helong Zhou, Xiliu Chen, Pian Ye, Bin Zhu, Shengsong He, Yongwen He, Shenghua Jie, Ping Wei, Jianao Zhang, Yinping Lu, Weixian Wang, Li Zhang, Ling Li, Fengqin Zhou, Jun Wang, Ulf Dittmer, Mengji Lu, Dongliang Yang Yu Hu, Xin Zheng, Longitudinal Characteristics of Lymphocyte Responses and Cytokine Profiles in the Peripheral Blood of SARS-CoV-2 Infected Patients, medRxiv, 2020 2020.02.16.20023671.
[148] M.A. Moni, P. Liò, Network-based analysis of comorbidities risk during an infection: SARS and HIV case studies, BMC Bioinf. 15 (2014) 333.
[149] L. Ren, R. Gonzalez, J. Xu, Y. Xiao, Y. Li, H. Zhou, J. Li, Q. Yang, J. Zhang, L. Chen, W. Wang, G. Vernet, G. Paranhos-Baccalà, Z. Wang, J. Wang, Prevalence of human coronaviruses in adults with acute respiratory tract infections in Beijing, China, J. Med. Virol. 83 (2) (2011) 291–297.
[150] R.E. Cone, J.J. Marchalonis, Cellular and humoral aspects of the influence of environmental temperature on the immune response of poikilothermic vertebrates, J. Immunol. 108 (4) (1972) 952–957.
[151] H.D. Jampel, G.W. Duff, R.K. Gershon, E. Atkins, S.K. Durum, Fever and immunoregulation. III. Hyperthermia augments the primary in vitro humoral immune response, J. Exp. Med. 157 (4) (1983) 1229–1238.
[152] N.J. Roberts Jr., K. Sandberg, Hyperthermia and human leukocyte function. II. Enhanced production of and response to leukocyte migration inhibition factor (LIF), J. Immunol. 122 (5) (1979) 1990–1993.
[153] W. Roszkowski, S. Szmigielski, M. Janiak, J.K. Wrembel, K. Roszkowski, W. Hryniewicz, Effect of hyperthermia on rabbit macrophages, Immunobiology 157 (2) (1980) 122–131.
[154] C.J. van Oss, D.R. Absolom, L.L. Moore, B.H. Park, J.R. Humbert, Effect of temperature on the chemotaxis, phagocytic engulfment, digestion and O2 consumption of human polymorphonuclear leukocytes, J. Reticuloendothel. Soc. 27 (6) (1980) 561–565.
[155] A. Deussen, [Hyperthermia and hypothermia. Effects on the cardiovascular system], Anaesthesist 56 (9) (2007) 907–911.
[156] K.E. Cooper, Some responses of the cardiovascular system to heat and fever, Can. J. Cardiol. 10 (4) (1994) 444–448.
[157] Hmly Herath, Jmhd Jayasundara, S.D.N. Senadhira, S.A.M. Kularatne, W.K.S. Kularatne, Spotted fever rickettsioses causing myocarditis and ARDS: a case from Sri Lanka, BMC Infect. Dis. 18 (1) (2018) 705.
[158] S. Miyamoto, T. Ito, S. Terada, T. Eguchi, H. Furubeppu, H. Kawamura, T. Yasuda, Y. Kakihana, Fulminant myocarditis associated with severe fever with thrombocytopenia syndrome: a case report, BMC Infect. Dis. 19 (1) (2019) 266.
[159] D. Morikawa, E. Hiraoka, K. Obunai, Y. Norisue, Myocarditis associated with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a case report and review of the literature, Am. J. Case Rep. 19 (2018) 978–984.
[160] S.A.M. Kularatne, M.M. Rajapakse, U. Ralapanawa, R. Waduge, Lpmmk Pathirage, Rpvj Rajapakse, Heart and liver are infected in fatal cases of dengue: three PCR based case studies, BMC Infect. Dis. 18 (1) (2018) 681.
[161] R.H. Chowdhury, S.M. Ahmed, M.N. Hasan, Dengue myocarditis: an important clinical entity to consider in dengue patient, Mymensingh Med. J. 28 (3) (2019) 708–711.
[162] I.K. Lee, W.H. Lee, J.W. Liu, K.D. Yang, Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients, Int. J. Infect. Dis. 14 (10) (2010) e919–22.
[163] J.Y. Chin, K.W. Kang, K.M. Moon, J. Kim, Y.J. Choi, Predictors of acute myocarditis in complicated scrub typhus: an endemic province in the Republic of Korea, Korean J. Intern. Med. 33 (2) (2018) 323–330.
[164] T. Yamamoto, T. Kenzaka, M. Matsumoto, R. Nishio, S. Kawasaki, H. Akita, A case report of myocarditis combined with hepatitis caused by herpes simplex virus, BMC Cardiovasc. Disord. 18 (1) (2018) 134.
[165] A. Prabha, Mohanan, P. Pereira, C.V. Raghuveer, Myocarditis in enteric fever, Indian J. Med. Sci. 49 (2) (1995) 28–31.
[166] A.K. Abdullah, J.K. Goel, M.A. Siddiqui, Systolic time intervals in febrile states, Heart J. 22 (5) (1981) 739–745.
[167] J. Weissinger, P. Wolf, C. Bloor, Serum enzyme abnormalities in swine associated with systemic infection and fever, Enzyme 25 (5) (1980) 342–345.
[168] K.L. Liem, D. Durrer, K.I. Lie, H.J. Wellens, Pericarditis in acute myocardial infarction, Lancet 2 (7943) (1975) 1004–1006.
[169] C.A. VILLEE, D.D. HAGERMAN, Effect of oxygen deprivation on the metabolism of fetal and adult tissues, Am. J. Physiol. 194 (3) (1958) 457–464.
[170] J.K. Yun, T.S. McCormick, R. Judware, E.G. Lapetina, Cellular adaptive responses to low oxygen tension: apoptosis and resistance, Neurochem. Res. 22 (4) (1997) 517–521.
[171] Jacqueline E. Tamis-Holland, Hani Jneid, Harmony R. Reynolds, Stefan Agewall, Emmanouil S. Brilakis, Todd M. Brown, Amir Lerman, Mary Cushman, Dharam J. Kumbhani, Cynthia Arslanian-Engoren, Ann F. Bolger, John F. Beltrame, Cardiology Council Clinical, Nursing Council Cardiovasc Stroke, Prevention Council Epidemiology, Res Council Quality Care Outcomes, Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the american heart association, Circulation 139 (18) (2019) E891–E908.
[172] M. Madjid, C.C. Miller, V.V. Zarubaev, I.G. Marinich, O.I. Kiselev, Y.V. Lobzin, A.E. Filippov, S.W. Casscells 3rd, Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects, Eur. Heart J. 28 (10) (2007) 1205–1210.
[173] Jeffrey C. Kwong, Kevin L. Schwartz, Michael A. Campitelli, Hannah Chung, Natasha S. Crowcroft, Timothy Karnauchow, Kevin Katz, Dennis T. Ko, Allison J. McGeer, Dayre McNally, David C. Richardson, Laura C. Rosella, Andrew Simor,

Marek Smieja, George Zahariadis, Jonathan B. Gubbay, Acute myocardial infarction after laboratory-confirmed influenza infection, N. Engl. J. Med. 378 (4) (2018) 345–353.
[174] M. Madjid, A.T. Connolly, Y. Nabutovsky, P. Safavi-Naeini, M. Razavi, C.C. Miller, Effect of high influenza activity on risk of ventricular arrhythmias requiring therapy in patients with implantable cardiac defibrillators and cardiac resynchronization therapy defibrillators, Am. J. Cardiol. 124 (1) (2019) 44–50.
[175] S. Kytömaa, S. Hegde, B. Claggett, J.A. Udell, W. Rosamond, J. Temte, K. Nichol, J.D. Wright, S.D. Solomon, O. Vardeny, Association of influenza-like illness activity with hospitalizations for heart failure: the atherosclerosis risk in communities study, JAMA Cardiol. 4 (4) (2019) 363–369.
[176] O. Vardeny, S.D. Solomon, Influenza vaccination: a one-shot deal to reduce cardiovascular events, Eur. Heart J. 38 (5) (2017) 334–337.
[177] M. Madjid, I. Aboshady, I. Awan, S. Litovsky, S.W. Casscells, Influenza and cardiovascular disease: is there a causal relationship? Tex. Heart Inst. J. 31 (1) (2004) 4–13.
[178] V.F. Corrales-Medina, M. Madjid, D.M. Musher, Role of acute infection in triggering acute coronary syndromes, Lancet Infect. Dis. 10 (2) (2010) 83–92.
[179] J.A. Regla-Nava, J.M. Jimenez-Guardeño, J.L. Nieto-Torres, T.M. Gallagher, L. Enjuanes, M.L. DeDiego, The replication of a mouse adapted SARS-CoV in a mouse cell line stably expressing the murine SARS-CoV receptor mACE2 efficiently induces the expression of proinflammatory cytokines, J. Virol. Methods 193 (2) (2013) 639–646.
[180] L. He, Y. Ding, Q. Zhang, X. Che, Y. He, H. Shen, H. Wang, Z. Li, L. Zhao, J. Geng, Y. Deng, L. Yang, J. Li, J. Cai, L. Qiu, K. Wen, X. Xu, S. Jiang, 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. 210 (3) (2006) 288–297.
[181] D.L. Mann, Inflammatory mediators and the failing heart: past, present, and the foreseeable future, Circ. Res. 91 (11) (2002) 988–998.
[182] M.L. DeDiego, J.L. Nieto-Torres, J.A. Regla-Nava, J.M. Jimenez-Guardeño, R. Fernandez-Delgado, C. Fett, C. Castaño-Rodriguez, S. Perlman, L. Enjuanes, Inhibition of NF-κB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival, J. Virol. 88 (2) (2014) 913–924.
[183] Guang Chen, Wu Di, Wei Guo, Yong Cao, Huang Da, Hongwu Wang, Tao Wang, Xiaoyun Zhang, Huilong Chen, Haijing Yu, Xiaoping Zhang, Minxia Zhang, Shiji Wu, Jianxin Song, Tao Chen, Meifang Han, Shusheng Li, Xiaoping Luo, Jianping Zhao, Qin Ning, Clinical and Immunologic Features in Severe and Moderate Forms of Coronavirus Disease 2019, medRxiv, 2020 2020.02.16.20023903.
[184] J.J. Zhang, X. Dong, Y.Y. Cao, Y.D. Yuan, Y.B. Yang, Y.Q. Yan, C.A. Akdis, Y.D. Gao, Clinical Characteristics of 140 Patients Infected With SARS-CoV-2 in Wuhan, China, Allergy, (2020).
[185] J. Górka, K. Polok, T. Iwaniec, K. Górka, A. Wludarczyk, J. Fronczek, P.J. Devereaux, J.W. Eikelboom, J. Musial, W. Szczeklik, Altered preoperative coagulation and fibrinolysis are associated with myocardial injury after non-cardiac surgery, Br. J. Anaesth. 118 (5) (2017) 713–719.
[186] Antoine Vieillard-Baron, Vincent Caille, Cyril Charron, Guillaume Belliard, Bernard Page, Francois Jardin, Actual incidence of global left ventricular hypokinesia in adult septic shock, Crit. Care Med. 36 (6) (2008) 1701–1706.
[187] Zongyu Wang, Hongliang Li, Gaiqi Yao, Xi Zhu, Impacts of sepsis-induced myocardial dysfunction on hemodynamics, organ function and prognosis in patients with septic shock, Zhonghua wei zhong bing ji jiu yi xue 27 (3) (2015) 180–184.
[188] G.M. McAlonan, A.M. Lee, V. Cheung, C. Cheung, K.W. Tsang, P.C. Sham, S.E. Chua, J.G. Wong, Immediate and sustained psychological impact of an emerging infectious disease outbreak on health care workers, Canadian journal of psychiatry, Can. Child Adolesc. Psychiatr. Rev. 52 (4) (2007) 241–247.
[189] P.S. Yip, Y.T. Cheung, P.H. Chau, Y.W. Law, The impact of epidemic outbreak: the case of severe acute respiratory syndrome (SARS) and suicide among older adults in Hong Kong, Crisis 31 (2) (2010) 86–92.
[190] Gordon J.G. Asmundson, Jonathon S. Abramowitz, Ashley A. Richter, Margaret Whedon, Health anxiety: current perspectives and future directions, Curr. Psychiatry Rep. 12 (4) (2010) 306–312.
[191] A.S. Nagaraja, N.C. Sadaoui, P.L. Dorniak, S.K. Lutgendorf, A.K. Sood, SnapShot: stress and disease, Cell Metab. 23 (2) (2016) 388-388.e1.
[192] Chenyun Liu, Yun-zhi Yang, Xiao Ming Zhang, Xu Xinying, Qing-Li Dou, Wen-Wu Zhang, The Prevalence and Influencing Factors for Anxiety in Medical Workers Fighting COVID-19 in China: A Cross-Sectional Survey, medRxiv, 2020 2020.03.05.20032003.
[193] Long Huang, Fu ming xu, Hairong Liu, Emotional Responses and Coping Strategies of Nurses and Nursing College Students During COVID-19 Outbreak, medRxiv, 2020 2020.03.05.20031898.
[194] Luna Sun, Zhuoer Sun, Lili Wu, Zhenwen Zhu, Fan Zhang, Zhilei Shang, Yanpu Jia, Jingwen Gu, Yaoguang Zhou, Yan Wang, Nianqi Liu, Weizhi Liu, Prevalence and Risk Factors of Acute Posttraumatic Stress Symptoms During the COVID-19 Outbreak in Wuhan, China, medRxiv, 2020 2020.03.06.20032425.
[195] L.K. Alexander, B.W. Keene, J.D. Small, B. Yount Jr., R.S. Baric, Electrocardiographic changes following rabbit coronavirus-induced myocarditis and dilated cardiomyopathy, Adv. Exp. Med. Biol. 342 (1993) 365–370.
[196] B.D. Anson, J.G. Weaver, M.J. Ackerman, O. Akinsete, K. Henry, C.T. January, A.D. Badley, Blockade of HERG channels by HIV protease inhibitors, Lancet 365 (9460) (2005) 682–686.
[197] C.V. Etchegoyen, G.A. Keller, S. Mrad, S. Cheng, G. Di Girolamo, Drug-induced QT interval prolongation in the intensive care unit, Curr. Clin. Pharmacol. 12 (4) (2017) 210–222.
[198] T.F. Simpson, J.W. Salazar, E. Vittinghoff, J. Probert, A. Iwahashi, J.E. Olgin, P. Ursell, A. Hart, E. Moffatt, Z.H. Tseng, Association of QT-Prolonging medications with risk of autopsy-defined causes of sudden death, JAMA Intern. Med. (2020).
[199] P. Gautret, J.C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V.E. Vieira, H.T. Dupont, S. Honoré, P. Colson, E. Chabrière, B. La Scola, J.M. Rolain, P. Brouqui, D. Raoult, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents (2020) 105949.
[200] C.Y. Chen, F.L. Wang, C.C. Lin, Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia, Clin. Toxicol. (Phila) 44 (2) (2006) 173–175.
[201] N.D. Morgan, S.V. Patel, O. Dvorkina, Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus, J. Clin. Rheumatol. 19 (5) (2013) 286–288.
[202] J.P. O'Laughlin, P.H. Mehta, B.C. Wong, Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine, Case Rep. Cardiol. 2016 (2016) 4626279.
[203] J. de Olano, M.A. Howland, M.K. Su, R.S. Hoffman, R. Biary, Toxicokinetics of hydroxychloroquine following a massive overdose, Am. J. Emerg. Med. 37 (12) (2019) 2264 e5-2264.e8.
[204] Y. Choi, H.S. Lim, D. Chung, J.G. Choi, D. Yoon, Risk evaluation of azithromycin-induced QT prolongation in real-world practice, Biomed Res. Int. 2018 (2018) 1574806.
[205] S.P. Sears, T.W. Getz, C.O. Austin, W.C. Palmer, E.A. Boyd, F.F. Stancampiano, Incidence of sustained ventricular tachycardia in patients with prolonged QTc after the administration of azithromycin: a retrospective study, Drugs Real World Outcomes 3 (1) (2016) 99–105.
[206] A. Kezerashvili, H. Khattak, A. Barsky, R. Nazari, J.D. Fisher, Azithromycin as a cause of QT-interval prolongation and torsade de pointes in the absence of other known precipitating factors, J. Interv. Card. Electrophysiol. 18 (3) (2007) 243–246.
[207] R. Pires dos Santos, R. Kuchenbecker, Azithromycin and the risk of cardiovascular death, N. Engl. J. Med. 367 (8) (2012) 774–775 author reply 775.
[208] S.S. Chugh, K. Reinier, T. Singh, A. Uy-Evanado, C. Socoteanu, D. Peters, R. Mariani, K. Gunson, J. Jui, Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study, Circulation 119 (5) (2009) 663–670.
[209] Zheyong Huang, Jiatian Cao, Yumeng Yao, Xuejuan Jin, Zhe Luo, Yuan Xue, Chouwen Zhu, Yanan Song, Ying Wang, Yunzeng Zou, Juying Qian, Kaihuan Yu, Hui Gong, Junbo Ge, The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension, Ann. Transl. Med. 8 (7) (2020) 430.
[210] J.H. Diaz, Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19, J. Travel Med. (2020).
[211] J.L. Sapp, W. Alqarawi, C.J. MacIntyre, R. Tadros, C. Steinberg, J.D. Roberts, Z. Laksman, J.S. Healey, A.D. Krahn, Guidance on minimizing risk of drug-induced ventricular arrhythmia during treatment of COVID-19: a statement from the canadian heart rhythm society, Can. J. Cardiol. (2020).
[212] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K.W. Davidson, D.P. Barnaby, L.B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J.N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area, Jama (2020).
[213] M. Arentz, E. Yim, L. Klaff, S. Lokhandwala, F.X. Riedo, M. Chong, M. Lee, Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State, Jama 323 (16) (2020) 1612–1614.
[214] G. Grasselli, A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, D. Cereda, A. Coluccello, G. Foti, R. Fumagalli, G. Iotti, N. Latronico, L. Lorini, S. Merler, G. Natalini, A. Piatti, M.V. Ranieri, A.M. Scandroglio, E. Storti, M. Cecconi, A. Pesenti, Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy, Jama 323 (16) (2020) 1574–1581.
[215] Christopher M. Petrilli, Simon A. Jones, Jie Yang, Harish Rajagopalan, Luke F. Donnell, Yelena Chernyak, Katie Tobin, Robert J. Cerfolio, Fritz Francois, Leora I. Horwitz, Factors Associated With Hospitalization and Critical Illness Among 4,103 Patients With COVID-19 Disease in New York City, medRxiv, 2020 2020.04.08.20057794.
[216] A.M. Dondorp, M. Hayat, D. Aryal, A. Beane, M.J. Schultz, Respiratory support in novel coronavirus disease (COVID-19) patients, with a focus on resource-limited settings, Am. J. Trop. Med. Hyg. (2020).
[217] Chaomin Wu, Xiaoyan Chen, Yanping Cai, Jia'an Xia, Xing Zhou, Sha Xu, Hanping Huang, Li Zhang, Xia Zhou, Chunling Du, Yuye Zhang, Juan Song, Sijiao Wang, Yencheng Chao, Zeyong Yang, Jie Xu, Xin Zhou, Dechang Chen, Weining Xiong, Lei Xu, Feng Zhou, Jinjun Jiang, Chunxue Bai, Junhua Zheng, Yuanlin Song, Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Intern. Med. (2020).
[218] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (3) (2020) 269–271.
[219] Yeming Wang, Dingyu Zhang, Du Guanhua, Du Ronghui, Jianping Zhao, Yang Jin, Fu Shouzhi, Ling Gao, Zhenshun Cheng, Lu Qiaofa, Hu Yi, Guangwei Luo, Wang Ke, Lu Yang, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Wang Yi, Dan Ding, Wu Feng, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu,

Gu Xiaoying, Xu Jiuyang, Lianhan Shang, Zhang Yi, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G. Hayden, Peter W. Horby, Bin Cao, Chen Wang, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, Lancet (2020).

[220] National Institutes of Health, NIH Clinical Trial Shows Remdesivir Accelerates Recovery From Advanced COVID-19, (2020) https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19.

[221] Gilead, Gilead Announces Results From Phase 3 Trial of Investigational Antiviral Remdesivir in Patients With Severe COVID-19-Study Demonstrates Similar Efficacy With 5- and 10-Day Dosing Durations of Remdesivir, (2020) (Accessed 2020/4/29 2020), https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19.