Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Consequences of COVID-19 on the cardiovascular and renal systems

Yuan Zhu [a, 1], Xiaoyi Zhang [a, b, 1], Zhiyong Peng [a, b, *]

[a] Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan, 430071, Hubei, China
[b] Clinical Research Center of Hubei Critical Care Medicine, Wuhan, Hubei, China

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1. Introduction

Coronavirus Disease 2019 (COVID-19), which is arisen from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, has become a global threat and challenge. As of 12 July 2022, there have been over 554 million confirmed cases and more than 6 million deaths [1]. Fever, cough, dyspnea, fatigue and diarrhea are reported to be common symptoms of COVID-19 in most patients [2–4]. Though known mainly for respiratory symptoms, the clinical spectrum of COVID-19 varies, from asymptomatic or mild presentation of upper respiratory tract infection, to multiple extrapulmonary manifestations related with the gastrointestinal, cardiovascular, dermatological, renal systems, etc. [5–9]. Shi et al. reported that COVID-19 patients with cardiac injury were much prone to develop other complications, including acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), electrolyte disturbance, etc, and also showed a higher mortality, suggesting cardiac injury as a potential death risk factor for COVD-19 patients [10]. AKI is another common complication that is associated with mortality and severity of COVID-19 [9,11]. Therefore, out of necessity, we are going to investigate the association between COVID-19 and dysfunction of cardiovascular and renal systems.

In the present review, we will summarize and discuss the consequences of COVID-19 on cardiovascular and renal systems from aspects of the possible pathophysiological mechanisms, risk factors, clinical manifestations, diagnosis and treatments, as well as prognosis.

2. Pathophysiological mechanisms

SARS-CoV-2 is a single-stranded RNA virus, which belongs to the *Coronaviridae* family [12]. Sharing about 80% sequence identity with SARS-CoV, SARS-CoV-2 enters the host cells through specific targeting and binding activities between the spike (S) protein and angiotensin-converting enzyme 2 (ACE2), the same mechanism as SARS-CoV [13–16]. The cellular serine protease TMPRSS2, which is helpful for further binding and fusion, also participates in this binding activity [15–18]. Gupta et al. had well concluded the possible pathophysiological mechanisms of COVID-19 as: (1) direct viral toxicity; (2) dysfunction of the renin-angiotensin-aldosterone system (RAAS); (3) endothelial cell damage and thrombosis; (4) dysregulation of the immune response [19]. To better illustrate the pathophysiological mechanisms of COVID-19 related cardiovascular and renal dysfunction, we are trying to state the possible mechanisms based on these aspects.

2.1. Direct toxicity of virus

SARS-CoV-2 primarily spreads through respiratory transmission [20]. As noted above, the binding of S protein to ACE2 is essential in the process of entry. SARS-CoV-2 is considered more pathogenic due to its increased binding affinity to ACE2 [15,21]. ACE2 protein is wildly expressed in multiple organs, including the small intestine, kidneys, heart and lung [22–24]. The wide distribution of ACE2 could explain the positive detection of SARS-CoV-2 in the specimens of feces, urine and sputum from patients with COVID-19 [25] and multiple extrapulmonary manifestations of COVID-19. In addition, CD147, which is expressed in the coronary tree, epicardial nerves, and renal tubular cells, has been identified to medicate SARS-CoV-2 entering host cells through endocytosis [26–28], making it reasonable for heart and kidneys being the potential targeting organs.

Viral particles of SARS-CoV-2 have been detected in heart and renal tissues, including myocardium, glomerular cells, proximal tubular epithelium, podocytes and distal tubules by electron microscopy [29–32]. Endocardial inflammation, cardiomegaly, and right ventricular dilatation were reported in patients who died with COVID-19 [32,33]. Necrosis of myocytes and interstitial tissue, and infiltration of macrophages and lymphocytes were also observed in COVID-19 patients by microscopic evaluation [33,34].

* Corresponding author. Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuhan, 430071, Hubei, China.
E-mail address: Pengzy5@hotmail.com (Z. Peng).
[1] These authors contribute equally.

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Histopathological findings in kidney of those infected also showed diffuse proximal tubule lesions, prominent erythrocyte aggregation and obstruction of peritubular and glomerular capillary loops [29]. These findings strongly support the direct viral toxicity of SARS-CoV-2 to heart and kidneys.

2.2. ACE2 and the renin-angiotensin-aldosterone system (RAAS)

ACE2 is not only a binding receptor for SARS-CoV-2 entering target cells, but also a negative regulator for the RAAS, a hormonal axis that is associated with blood pressure, sodium retention, potassium excretion, pro-inflammatory and pro-fibrotic effects, as well as tissue remodeling [35,36]. Angiotensin II (Ang II) is one of the main key active products of the RAAS, and participates in all classical functions mentioned above by binding to the AT_1 receptor [35]. ACE2 acts as a negative regulator of the RAAS by: (1) limiting the amount of Ang II by transferring angiotensin I into angiotensin (1–9) to reduce the substrate and the production of Ang II; (2) countering the functions of Ang II by converting Ang II to angiotensin (1–7), which counteract the actions of the AT_1 receptor by binding to the Mas receptor or the AT_2 receptor [35,37].

Competitive binding of the coronavirus to ACE2 will lead to downregulation of ACE2, resulting in accumulation of Ang II and activation of the RAAS, leading to further renal and heart hypoperfusion, dysfunction, fibrosis and tissue remodeling [37–40]. Ang II also acts as a pro-inflammatory cytokine, leading to endothelial dysfunction, vascular hyperpermeability, upregulation of vascular endothelial growth factor (VEGF) and activation of circulating immune cells [40–43]. It has been reported that activation of the RAAS is associated with kidney and cardiovascular injury via inflammation and fibrosis [39,41–44]. This association between the RAAS activation and AKI was further confirmed in patients with COVID-19 [45]. However, the interaction between the RAAS and SARS-CoV-2 still requires more detailed researches.

2.3. Endothelial cell damage

Vascular endothelium is indispensable to maintain vascular homeostasis through regulation of vascular tone, immune response, inflammation, as well as the balance of thrombotic and fibrinolytic pathways [46,47]. Its dysfunction is demonstrated to be associated with inflammation, vasoconstriction, tissue ischemia, and thrombosis [48]. Endothelial injury is a common pathological change associated with the intracellular SARS-CoV-2 virus in COVID-19 patients [49,50]. Observed diffuse endothelial inflammation is suspected to be linked to direct viral toxicity or recruitment of immune cells [50]. ACE2 is presented on vascular endothelial cells and arterial smooth muscle cells [24], making it reasonable for the observation of virus particles within renal and heart endothelial cells in COVID-19 patients [32,50]. Notably, ACE2 staining was much more positive in vascular endothelium than in other part of kidney tissues [24], suggesting that the endothelium may be the most vulnerable in defending viral attack, and secondary subsequent endotheliitis may be the dominant mechanism of renal injury and other organ damage in SARS-CoV-2.

Furthermore, exposure of sub-endothelial collagen caused by endothelial injury will lead to platelet aggregation and subsequent thrombosis formation [51]. A multicenter cohort study showed that D-dimer, fibrinogen, and Von Willebrand (vWF) activity were all considerably elevated in critically ill patients with COVID-19 [52]. Autopsy reports reported the existences of deep venous thrombosis (DVT) and pulmonary embolism formation (PEF) in patients with COVID-19 [31,33]. Fibrin thrombus in renal glomerular capillary loops was also observed in patients with COVID-19, which was thought to be the result of severe endothelial injury [29], and to be an important mechanism of AKI [53].

It's known that children aren't susceptible to SARS-CoV-2, and are less likely to develop severe complications than adult patients. Scientists believe the difference between children and adults can be explained by the different condition of vessels [54]. In adult population, patients with pre-existing diseases that compromise the endothelium, such as diabetes and hypertension, always developed into severe COVID-19 and poor outcome [55,56]. These evidences strongly suggest us to focus on the endothelium injury.

2.4. Dysregulation of immune response

The unbalanced immune/anti-immune response is one crucial characteristic of COVID-19. Increased pro-inflammatory cytokines and decreased lymphocytes are two main features of immune response dysregulation [57–59]. The former was associated with the immune cell activation and subsequent cytokine storm in patients with COVID-19 [60], as occurred in H7N9 influenza, SARS and MERS infections [61–63]. In fact, a new process, known as viral sepsis, was assumed to be linked to multiple organ dysfunction (MODS), in patients with COVID-19 [64]. Once activated, immune cells, such as monocytes and macrophages, can release quantities of pro-inflammatory cytokines and chemokines [65], such as TNF-α, IFN-α, IL-1β, IL-6, IL-8, GM-CSF and MCP-1, which were increased in patients with COVID-19, proving the involvement of cytokine storm [57]. If not treated adequately in time, cytokine storm could lead to systemic inflammation, MODS, and even death [66], and was associated with severity of disease, as critically ill COVID-19 patients were reported to have higher levels of those cytokines [57]. Macrophages and T lymphocytes found in the tubulointerstitium, in addition to the complement membrane-attack complex (MAC) found on tubules or glomeruli, suggested the participation and activation of immune system in renal damage in COVID-19 [67].

Lymphopenia is another common clinical manifestation of COVID-19 and has been reported as a risk factor for severe COVID-19 [58]. Reduction of lymphocytes is thought to be associated with direct viral toxicity via CD147, lymphatic organ damage and cell apoptosis resulted from increased pro-inflammatory cytokines [58,68–70]. Increased pro-inflammatory cytokines and decreased lymphocytes strongly suggested the presence of dysregulation of immune system in the pathogenesis of COVID-19, and are also expected to be a therapeutic target [53].

2.5. Other possible mechanisms

The side effects of antiviral drugs during the treatment of COVID-19 might induce organ toxicity. Hydroxychloroquine and azithromycin were reported to be associated with prolonged QT interval and drug-induced torsades de pointes, leading to high risk of malignant arrhythmia and cardiac death [71]. Other drugs, including antibiotics, antiviral therapy or traditional medicine, are also related to renal injury, especially tubular injury and acute interstitial nephritis during the treatment in other settings [72].

Severe COVID-19 patients usually have impaired respiratory function, which often induces hypoxia and insufficient oxygen supply. Considerable fluid losses, resulting from hyperpyrexia and diarrhea, also contributed to volume depletion and perfusion reduction, causing cellular ischemia and hypoxia damage. Meanwhile, systemic inflammatory condition, ROS produced during hypoxia, combined with excessive anxiety and stress increased the oxygen demand of heart. Unbalanced myocardial oxygen supply and demand would lead to further deterioration of cardiac function [73]. The neutrophil activation and increased circulating neutrophil extracellular traps (NETs) in COVID-19 indicated the role of oxidative stress in the onset of COVID-19 [74]. Besides, patients with

ARDS are inherently prone to have AKI and atrial arrhythmias, as complications of mechanical ventilation [75,76]. Proteinuria, a manifestation of COVID-19, can also cause secondary renal damage [77]. All of the evidence highlighted the existence and significance of the indirect mechanisms of cardiovascular and renal dysfunction related to COVID-19.

3. Risk factors

3.1. Risk factors for COVID-19 related cardiovascular dysfunction

A cohort study from New York reported that atrial arrhythmia was more common in patients receiving mechanical ventilation than in those who didn't (17.7% vs 1.9%), implying mechanical ventilation may act as a risk factor for arrhythmia [76]. Cardiac arrhythmia, including new-onset atrial fibrillation, heart block, and ventricular arrhythmias, was also reported to be associated with disease severity of COVID-19, as the incidence of cardiac arrhythmia was higher among ICU patients than among normal hospitalized patients (44% vs 17%) [4]. The complications that always combined with cardiovascular lesions including diabetes, hypertension, and pre-existing CVD are also related to severity of COVID-19 [78,79].

3.2. Risk factors for COVID-19 related renal dysfunction

The related risk factors were well summarized in the consensus report of the 25th ADQI workgroup [53]. Apart from demographic characteristics and other risk factors (leukocytosis, lymphopenia, ventilation, nephrotoxic drugs and so on), comorbidities including diabetes, hypertension, CVD, congestive heart failure and chronic kidney disease are considered as risk factors for COVID-19 related AKI [53]. All of these comorbidities could lead to subsequent renal damage [80–82]. A postmortem study of patient died with COVID-19 reported that endothelial cell swelling with foamy degeneration, which appeared in older patients usually with hypertension or diabetes, was observed in glomeruli [29]. Thus, the susceptibility of these populations may be associated with endothelial injuries and microcirculation disturbances, which are common in patients with diabetes, hypertension or CVD [83,84].

4. Clinical manifestations and diagnosis

4.1. Cardiovascular dysfunction and diagnosis

Cardiovascular manifestations, including arrhythmia, acute cardiac injury, heart failure, and cardiomyopathy, as well as thromboembolism, are common clinical features in COVID-19 [7,10,57]. Myocardial injury was reported in 20–30% of COVID-19 inpatients, with a higher rate (55%) in patients with pre-existing CVD [7,10]. According to a multicenter cohort research, myocardial injury was observed in 62% of hospitalized COVID-19 patients, who had more ECG and echocardiographic abnormalities, as well as higher inflammatory biomarkers [85].

Diagnosis of cardiovascular dysfunction or cardiac injury can be done through several approaches. Troponin T was usually used to diagnose acute cardiac injury, if the serum level of it exceeded the 99th percent upper reference limit [10,57]. Other biomarkers, such as creatine kinase-myocardial band (CK-MB), myoglobin, and N-terminal pro-brain natriuretic peptide (NT-proBNP), which were reported to be elevated in COVID-19 and associated with severity and mortality of COVID-19 [7,86–90], can also be used as indicators for acute cardiac injury. Apart from these laboratory tests, electrocardiographic (ECG), echocardiogram, and cardiovascular magnetic resonance (CMR) were all useful complementary examinations to help diagnosis, monitor, and perhaps predict prognosis in COVID-19 patients with cardiac involvement [10,91,92]. The abnormal ECG findings, such as atrial fibrillation, ventricular arrhythmias, left ventricular hypertrophy, QT interval prolongation, and ST segment and T wave changes were reported in COVID-19 patients with cardiac injury [10,93–95]. In some cases, it's hard to interpret the elevation of cardiac troponin levels or ECG changes, because these changes may be unspecific or due to a wide range of cardiac insults. Echocardiogram is portable, safe, and usually more readily deployed, and it is necessary in monitoring hemodynamics and evaluating cardiac structures [96]. CMR is also an excellent tool for evaluating cardiac function and cardiovascular abnormalities [97].

4.1.1. Arrhythmia

Arrhythmia is a common clinical manifestation in COVID-19. During hospitalization of COVID-19, the incidence of malignant arrhythmia was higher in patients with high TnT levels, and arrhythmia is more common among COVID-19 patients in ICU [4,7,98]. There was no evidence of direct association between COVID-19 and arrhythmia so far. According to previous experience, Electrolyte disorder, hypoxia, inflammatory response, stress and anxiety all contributed to the incidence of cardiac arrhythmia [98–100]. In addition, drug interactions, such as azithromycin and hydroxychloroquine, lopinavir and ritonavir may also lead to arrhythmia [101,102]. Thus, ECG should be closely monitored in patients with potential myocardial injury for early intervention.

4.1.2. Acute cardiac injury and heart failure

Acute myocardial injury is one the most commonly reported cardiovascular complications in COVID-19. Previous studies revealed that 8–28% of COVID-19 patients developed acute myocardial injury characterized by the changes on ECG, and the elevation of cardiac injury biomarkers, including troponin, NT-proBNP, and myoglobin, etc. [7,57]. The mechanisms underlying cardiac injury may be concluded as direct myocardial injury of the virus, systemic inflammatory response, myocardial oxygen demand supply mismatch as described above [103]. Myocarditis is a common form of myocardial injury reported in COVID-19 patients, and could be featured by macrophage and mononuclear infiltration in interstitium and endocardium [104]. In addition, cardiac tamponade complicating myo-pericarditis was also reported [105].

According to a study, heart failure was reported in 23% of all hospitalized COVID-19 patients, and half of non-survivors developed heart failure [106]. Similar to the mechanisms of acute cardiac injury, the onset of heart failure might be caused by the direct viral injury and the systemic inflammation response. Besides, pulmonary embolism formation under the hypercoagulable state during disease process may also cause acute right ventricular failure [107].

4.1.3. Stress-induced cardiomyopathy

Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy (TCM), has a dramatic clinical presentation, usually mimicking the acute myocardial infarction and could be induced by physical stress [108]. Recently, a 67-year-old woman with TCM secondary to COVID-19 infection was reported, in which case, marked repolarization abnormalities on ECG in the absence of ongoing severe cardiovascular problems were observed [109]. Another case report also described a TCM, which was resulted from co-infection of COVID-19 and influenza A [110]. It is noteworthy that in patients with elevated level of cardiac injury biomarkers, consideration of stress-induced cardiomyopathy must not be ignored.

4.1.4. Thromboembolism

The direct viral injury to endothelium and systemic inflammatory responses during the disease process break the balance

between pro-thrombotic and anti-thrombotic properties of the endothelium, thus predisposing patients to a pro-thrombotic state and triggering the activation of coagulation. According to recent researches, hemostatic abnormalities associated with COVID-19 comprised elevated D-dimer, prolonged prothrombin time (PT), increased international normalized ratio (INT), and elevated thrombin time (TT) [111–113]. The pro-thrombotic condition could increase the risk of both arterial thrombosis and venous thrombus embolism (VTE), which include pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), as reported in severe COVID-19 patients [114,115]. According to a recent cohort study, 20% of COVID-19 inpatients developed VTE [116]. All of these necessitated the demand of antithrombotic prophylaxis in patients at high risk of VTE. Tang et al. found no difference of 28-day mortality between heparin users and nonusers. However, in patients with sepsis-induced coagulopathy scoring $\geq$4 or D-dimer more than 6 times the upper limit of normal, the 28-day mortality was lower in heparin users than nonusers [117]. Platelet counts have been reported to be associated with respiratory function in COVID-19, and antiplatelet therapy has shown its effectiveness in improving hypoxemia and helping ventilator weaning [118,119].

4.2. COVID-19 related renal dysfunction and diagnosis

AKI is a common complication in patients with COVID-19, and is associated with mortality and severity of COVID-19 [9,11]. Renal dysfunction in COVID-19 is not limited to AKI, but also includes other clinical manifestations, including proteinuria (43.9%), hematuria (26.7%), increased creatinine (13.1%) and blood urea nitrogen (14.4%), as it was reported in patients with COVID-19 [9]. According to the ADQI workgroup recommendation, the KDIGO criteria based on serum creatinine level and urine output, was nominated for the diagnosis and report of AKI [53]. Urinalysis can also not be ignored for its role in diagnosis of proteinuria and hematuria. Renal injury biomarkers, such as cystatin C, α_1-microglobulin, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 and IL-18, were also reported to be helpful in the early detection of AKI and predicting subsequent deterioration of renal function in patients with septic AKI [120], and may play the same role in COVID-19 related AKI.

4.2.1. AKI

AKI is a common complication in patients with COVID-19, and also be identified as a death risk factor for COVID-19 patients [9,11]. The incidence of AKI among COVID-19 patients is reported higher than among COVID-19 negative patients [121], varying from 3% to 56.9% [4,75,104,121]. Among critically ill COVID-19 patients during the first 7 days in ICU, the incidence of AKI is approximately 80%, much higher than 36.6% in normal population [11,75]. The kidney injury was thought to be associated with high co-expression of ACE2 and TMPRSS on podocytes and proximal straight tubule cells [122], and the direct viral effects on these two kinds of cells are suspected to be one of the main causes of AKI in patients with COVID-19 [122].

4.2.2. Proteinuria

The reported incidence of proteinuria in COVID-19 inpatients ranged between 43.9% and 87% [9,75,123]. Podocytes and proximal straight tubule cells play vital roles in urine filtration reabsorption and excretion, and are identified to be host cells of SARS-CoV-2 [122,124]. Damage to podocytes often leads to proteinuria, a common characteristic of most glomerular diseases [124,125]. Podocytes assist in maintaining the glomerular filtration barrier. Podocytes are bridged by slit diaphragm, which is the component of the glomerular basement membrane (GBM), along with the actin cytoskeleton and cell adhesion molecules [124,125]. Damages to these components often result in proteinuria. And proteinuria, in turn, may cause secondary renal damage by exerting a direct toxic effect on renal tubular cells and promoting renal fibrosis over time [77].

4.2.3. Hematuria

Hematuria is another frequent clinical feature of renal injury. Reported incidence of hematuria in COVID-19 varies from 26.7% to 40.9% [9,75]. In most cases, hematuria is related to glomerular injury, especially the defects of GBM [126,127]. Recently, the interaction of renal inflammation with glomerular hematuria has been noticed. IgA nephropathy (IgAN) is the most common primary glomerulonephritis and the most common cause of glomerular hematuria [127,128]. In an experimental model of IgAN, the inflammatory and incidence of hematuria were decreased after treating with an IgA1 protease [129]. Evidence from several case reports also validated potential association between IgAN and SARS-CoV-2 vaccination [130,131]. However, it's too soon to draw a conclusion that hematuria is related to the renal inflammation and complement deposition caused by SARS-CoV-2 infection, as sparse evidence has been found.

4.2.4. Increase of serum creatinine and blood urea nitrogen

Serum creatinine and blood urea nitrogen are both indicators for renal function, and usually increase when GBM has been damaged and glomerular filtration rate (GFR) has been decreased [132,133]. Increased serum creatinine and blood urea nitrogen were observed in 13.1% and 14.4% of patients with COVID-19, separately [9]. Serum creatinine is the most commonly used biomarker of renal injury. Serum creatinine and blood urea nitrogen are both formed during protein metabolism, and are almost completely eliminated through the kidneys [133]. Creatinine has a low molecular weight and may cross GBM freely. Thus, the increase of serum creatinine level reflects damaged GBM and decreased GFR in COVID-19 patients.

4.2.5. Increase of kaliuresis

The Kidneys play an essential role in maintaining the fluid and electrolyte balance. Hypokalemia is a complication associated with continuous real potassium loss. One cohort study [99] of 175 patients of COVID-19 reported that 55% patients developed hypokalemia (18% with severe hypokalemia), whereas the proportion of hypokalemia among critically ill patients reached 85%. The authors also mentioned that hypokalemia might be associated with enhanced potassium excretion, which was secondary to activation of the RAAS, caused by the reduction in ACE2 activity [99,134]. However, other researchers believed that hypokalemia might also be secondary to diarrhea induced by SARS-CoV-2, the use of diuretics or other drugs, and cannot be simply explained by activation of the RAAS, at least more evidence should be presented [135].

5. Treatments

5.1. Antiviral therapy

SARS-CoV-2 infection have been broadly described as one of the most common causes of cardiovascular, renal, and other complications [26,29–32,42]. Hence the antiviral therapy is a very necessary part of alleviating extrapulmonary manifestations. Remdesivir, a nucleotide analogue prodrug which has been considered as the most promising antiviral drug for COVID-19, has shown its superiority in shortening the time to recovery and clinical improvement in inpatients with COVID-19 [136–138], and has been granted for COVID-19 to meet the urgent demand for treatment of inpatients by the FDA [139,140]. Other monoclonal antibodies, such

as ritonavir-boosted nirmatrelvir, bebtelovimab, and molnupiravir, were also approved to be used in patients with COVID-19 [141]. Tixagevimab-cilgavimab, a neutralizing monoclonal antibody combination, also reported to be helpful in reducing mortality in COVID-19 patients [142]. However, lopinavir—ritonavir, which is typically used against HIV, shown no benefit in treating COVID-19 compared with standard treatment [143]. Although some studies have shown that antiviral therapy has a certain degree of effect, more large-scale randomized and placebo-controlled clinical trials are required to further verify.

Chloroquine and hydroxychloroquine, which can potentially block the entry of virus into cells, and mediate immunomodulatory effects, have now been widely lavished as effective agents for COVID-19 [7]. Treatment with hydroxychloroquine was significantly associated with a reduction/disappearance of viral load [144], and showed its highly effectiveness in reducing the mortality of severe COVID-19 patients [145]. However, no evidence, which supported the role of hydroxychloroquine administration in reducing the composite endpoint of intubation or death, was found [146]. A meta-analysis reconfirmed this conclusion, and further pointed out that the use of chloroquine and hydroxychloroquine even increased the adverse events [147].

5.2. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) treatment

ACE2 is the receptor for SARS-CoV-2. Cardiac pericytes, podocytes and proximal tubule cells with high expression of ACE2 were considered as target cells of SARS-CoV-2 [122,148]. More importantly, patients with underlying heart failure showed increased ACE2 expression, indicating a higher risk of heart attack and critically ill condition, once these patients were infected by SARS-CoV-2 [149]. ACEI/ARB treatment have shown effectiveness in improving virus-induced lung damage in animal models of SARS-CoV-2 infection [14]. Inpatient use of ACEI/ARB was also associated with lower risk of all-cause mortality compared with nonusers in COVID-19 [150]. A population-based case-control study also confirmed the safety of ACEI/ARB, and reported no evidence that ACEI/ARB modified susceptibility to COVID-19 [151]. The American Heart Association recommended that patients with hypertension should continue to use ACEIs, ARBs, or other RAS antagonists except for clinical reasons rather than COVID-19 [152]. However, hypotension and decreased filtration fraction are common adverse effects of ACEI/ARB administration that could cause or exacerbate AKI, thus the application of ACEI/ARB in COVID-19 patients with potential risk of AKI should be fully considered [53].

5.3. Anti-inflammatory, antioxidant and vitamin supplement

Cytokine storm plays an important role in COVID-19 myocardial injury [153]. Available evidence showed non-steroidal anti-inflammatory drugs may be associated with cardiovascular outcomes and nephrotoxicity, but so far, no evidence relating specifically to people with COVID-19 has been found [154–156]. Oxidative stress was thought to participated in the course of COVID-19, and new therapeutic approach [74]. Thus, antioxidants such as N-acetyl-l-cysteine in combination with elastase inhibitors were recommended to be applied in patients with severe COVID-19. Vitamins, such as Vitamin D and Vitamin C, as well as other supplements might also be beneficial in treating COVID-19 [157,158].

5.4. Immunomodulatory therapy

Corticosteroid is not recommended to routinely treat all COVID-19 patients because it may aggravate lung damage [159]. However, considering the effects of cytokine storm in COVID-19, immunosuppressive therapy that suppresses the hyperinflammatory response may be beneficial [160]. Good news came that methylprednisolone was beneficial in reducing mortality in severe COVID-19 patients [161]. Another clinical research also reported that dexamethasone reduced the 28-day mortality of hospitalized COVID-19 patients receiving either invasive mechanical ventilation or oxygen alone [162].

The use of convalescent plasma may also benefit for severe COVID-19 patient, including direct neutralization of virus, control of overactive immune system and immune regulation of hypercoagulable state [163]. This may be a potential method for the treatment of COVID-19 patients with MODS including renal and cardiac injury. In some cytokines, IL-6 contributes to the development of cytokine storm and may play a vital role in extrapulmonary manifestations associated with SARS-CoV-2 [164]. Anti-IL-6 antibody treatment has reported to be beneficial in treating COVID-19 [161].

5.5. Extracorporeal membrane oxygenation (ECMO) therapy

ECMO is an evidence-based therapy method for ARDS, but it is not frequently used and is usually available in specialized centers [165]. A case reported that a patient with SARS-CoV-2 infection and cardiogenic shock regained hemodynamic stability after ECMO treatment for 7 days [166]. The clinical application value of ECMO in reducing mortality has been confirmed [167], but due to the large amounts of resources required to provide and the limited availability of these resources, it can only play a limited role in the current pandemic. Before applying ECMO to treat the patients with COVID-19 and cardiac injury, whether the patient's other comorbidities are suitable for ECMO should be considered [168].

5.6. Renal replacement treatment (RRT) and other new approaches

So far, there are no guidelines for the timing, patterns and parameters setting of renal replacement treatment (RRT) in treating COVID-19 related AKI, but rather previous clinical practice experience as a guide. It was reported that ventilation was one risk factor for AKI. Specifically, 90% of patients with mechanical ventilation developed AKI, and over half of the onset of AKI occurred within 24 h of intubation [75], suggesting early intervention and aggressive treatment for lung injury may decrease the incidence of AKI by reducing the demand for ventilation. Soluble urokinase receptor (SuPAR) was found to be predictive for COVID-19 related AKI and dialysis need [169]. It may serve as an indicator for COVID-19 related AKI. Scientists around the world are working on promising new therapies for COVID-19 related AKI. Clinical trials of cell therapy (SBI-101 therapy), sodium bicarbonate, and angiotensin 1-7 (TXA 127) and other promising therapies are ongoing in COVID-19 patients with AKI (NCT04445220; NCT04655716; NCT04401423).

Overall, vaccines are still the most promising way to cut down the incidence of COVID-19 related cardiac and renal injury, through reduced overall morbidity of COVID-19. Although no effective treatment has yet been obtained, early recognition and intervention can still help reduce mortality and improve the outcome of COVID-19 patients with AKI.

6. Prognosis

There isn't much information and data on the prognosis of patients with COVID-19 related cardiac and renal injury. Based on current evidences, patients with COVID-19 related cardiovascular and renal dysfunction have a poor prognosis. According to a review of 8 studies reporting totally 847 in-hospital cardiac arrest cases of

COVID-19 patients, the in-hospital mortality was as extremely high as 91.7% [170]. In 133 patients with COVID-19 receiving veno-venous ECMO, just half patients (54%) survived until day 30 after the implantation [171]. Although, study reported that symptoms of proteinuria, hematuria and AKI were often resolved after 3 weeks of onset [172]. Another observation study reported that, compared with COVID-19 negative patients, COVID-19 patients with AKI had less renal recovery, and those with stage 3 AKI were much more likely to experience in-hospital death [121]. It was reported that 7.3% of COVID-19 patients without AKI died, and the mortality of those with AKI (stage 1–3) not receiving dialysis and AKI receiving dialysis were extremely high as 46.4% and 79.3%, respectively [173]. In COVID-19 related AKI patients who received RRT, the outcomes were not so satisfying (63.3% of patients died) [174]. In patients with COVID-19 related AKI, only 30% recovered from renal injury and discharged alive [175]. These evidences generally point to a poor prognosis of COVID-19 related cardiovascular and renal injury, and suggest the importance of early identification and treatment of COVID-19 related organ lesions.

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CRediT authorship contribution statement

Yuan Zhu: Investigation, Writing – original draft, Writing – review & editing, Visualization. **Xiaoyi Zhang:** Methodology, Investigation, Writing – original draft. **Zhiyong Peng:** Conceptualization, Writing – review & editing, Supervision.

References

[1] World Health Organization. WHO coronavirus disease (COVID-19) dashboard [Available from: https://covid19.who.int/; 2022.
[2] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.
[3] Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020;5(7):831–40.
[4] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. JAMA 2020;323(11):1061–9.
[5] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323(13):1239–42.
[6] Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115(5):766–73.
[7] Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5(7):811–8.
[8] Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol 2020;34(5):e212–3.
[9] Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97(5):829–38.
[10] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in wuhan, China. JAMA Cardiol 2020;5(7):802–10.
[11] Joseph A, Zafrani L, Mabrouki A, et al. Acute kidney injury in patients with SARS-CoV-2 infection. Ann Intensive Care 2020;10(1):117.
[12] The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5(4):536–44.
[13] Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3.
[14] Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–74.
[15] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2).
[16] Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4.
[17] Glowacka I, Bertram S, Müller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol 2011;85(9):4122–34.
[18] Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 transmission and pathogenesis. Trends Immunol 2020;41(12):1100–15.
[19] Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26(7):1017–32.
[20] Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. Ann Intern Med 2021;174(1):69–79.
[21] Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367(6483):1260–3.
[22] Tipnis SR, Hooper NM, Hyde R, et al. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem 2000;275(43):33238–43.
[23] Li M-Y, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 2020;9(1):45.
[24] Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203(2):631–7.
[25] Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA 2020;323(18):1843–4.
[26] Wang K, Chen W, Zhang Z, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal Transduct Targeted Ther 2020;5(1):283.
[27] Kosugi T, Maeda K, Sato W, et al. CD147 (EMMPRIN/Basigin) in kidney diseases: from an inflammation and immune system viewpoint. Nephrol Dial Transplant 2015;30(7):1097–103.
[28] Maccio U, Zinkernagel AS, Shambat SM, et al. SARS-CoV-2 leads to a small vessel endotheliitis in the heart. EBioMedicine 2021;63:103182.
[29] Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98(1):219–27.
[30] Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 2020;383(6):590–2.
[31] Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173(4):268–77.
[32] Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020;22(5):911–5.
[33] Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020;8(7):681–6.
[34] Escher F, Pietsch H, Aleshcheva G, et al. Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Fail 2020;7(5):2440–7.
[35] Mirabito Colafella KM, Bovée DM, Danser AHJ. The renin-angiotensin-aldosterone system and its therapeutic targets. Exp Eye Res 2019;186:107680.
[36] Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1-7) in regulation of cardiovascular function. Am J Physiol Heart Circ Physiol 2005;289(6):H2281–90.
[37] Patel VB, Zhong J-C, Grant MB, et al. Role of the ACE2/angiotensin 1-7 Axis of the renin-angiotensin system in heart failure. Circ Res 2016;118(8):1313–26.
[38] Glowacka I, Bertram S, Herzog P, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol 2010;84(2):1198–205.
[39] Zhong J, Basu R, Guo D, et al. Angiotensin-converting enzyme 2 suppresses pathological hypertrophy, myocardial fibrosis, and cardiac dysfunction. Circulation 2010;122(7).
[40] Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med 2010;2(7):247–57.
[41] Ruiz-Ortega M, Esteban V, Rupérez M, et al. Renal and vascular hypertension-induced inflammation: role of angiotensin II. Curr Opin Nephrol Hypertens 2006;15(2).
[42] Kitayama H, Maeshima Y, Takazawa Y, et al. Regulation of angiogenic factors in angiotensin II infusion model in association with tubulointerstitial injuries. Am J Hypertens 2006;19(7):718–27.
[43] Welch WJ. Angiotensin II-dependent superoxide: effects on hypertension and vascular dysfunction. Hypertension 2008;52(1):51–6.
[44] Dudoignon E, Dépret F, Legrand M. Is the renin-angiotensin-aldosterone system good for the kidney in acute settings? Nephron 2019;143(3):179–83.
[45] Dudoignon E, Moreno N, Deniau B, et al. Activation of the renin-angiotensin-aldosterone system is associated with Acute Kidney Injury in COVID-19. Anaesth Crit Care Pain Med 2020;39(4):453–5.
[46] Godo S, Shimokawa H. Endothelial functions. Arterioscler Thromb Vasc Biol 2017;37(9):e108–14.
[47] Siddiqi HK, Libby P, Ridker PM. COVID-19 - a vascular disease. Trends

Cardiovasc Med 2021;31(1):1–5.
[48] Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003;23(2):168–75.
[49] Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in covid-19. N Engl J Med 2020;383(2):120–8.
[50] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234):1417–8.
[51] Yau JW, Teoh H, Verma S. Endothelial cell control of thrombosis. BMC Cardiovasc Disord 2015;15:130.
[52] Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020;46(6):1089–98.
[53] Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16(12):747–64.
[54] Cyranoski D. Why children avoid the worst coronavirus complications might lie in their arteries. Nature 2020;582(7812):324–5.
[55] Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in lombardy, Italy. JAMA Intern Med 2020;180(10):1345–55.
[56] Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146(1):110–8.
[57] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.
[58] Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Targeted Ther 2020;5(1):33.
[59] Liu Y, Li Y, Xu D, et al. Severe COVID-19: immunosuppression or hyperinflammation? Shock 2021;56(2):188–99.
[60] Zhang D, Guo R, Lei L, et al. Frontline Science: COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes. J Leukoc Biol 2021;109(1):13–22.
[61] Wang Z, Zhang A, Wan Y, et al. Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection. Proc Natl Acad Sci U S A 2014;111(2):769–74.
[62] Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. Cytokine Growth Factor Rev 2008;19(2):121–32.
[63] Kim ES, Choe PG, Park WB, et al. Clinical progression and cytokine profiles of Middle East respiratory syndrome coronavirus infection. J Kor Med Sci 2016;31(11):1717–25.
[64] Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020;395(10235):1517–20.
[65] Burdo TH, Walker J, Williams KC. Macrophage polarization in AIDS: dynamic interface between anti-viral and anti-inflammatory macrophages during acute and chronic infection. J Clin Cell Immunol 2015;6(3).
[66] Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383(23):2255–73.
[67] Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 infection. Nat Commun 2021;12(1):2506.
[68] Liao Y-C, Liang W-G, Chen F-W, et al. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol 2002;169(8):4288–97.
[69] Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827.
[70] Helal MA, Shouman S, Abdelwaly A, et al. Molecular basis of the potential interaction of SARS-CoV-2 spike protein to CD147 in COVID-19 associated-lymphopenia. J Biomol Struct Dyn 2020.
[71] Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med 2020;26(6):808–9.
[72] Welch HK, Kellum JA, Kane-Gill SL. Drug-associated acute kidney injury identified in the United States food and drug administration adverse event reporting system database. Pharmacotherapy 2018;38(8):785–93.
[73] Peng W, Wu H, Tan Y, et al. Mechanisms and treatments of myocardial injury in patients with corona virus disease 2019. Life Sci 2020;262:118496.
[74] Laforge M, Elbim C, Frère C, et al. Tissue damage from neutrophil-induced oxidative stress in COVID-19. Nat Rev Immunol 2020;20(9):515–6.
[75] Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98(1):209–18.
[76] Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of covid-19 in New York city. N Engl J Med 2020;382(24):2372–4.
[77] Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? J Am Soc Nephrol 2006;17(11):2974.
[78] Wu J, Zhang J, Sun X, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. Diabetes Obes Metabol 2020;22(10):1907–14.
[79] Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. Allergy 2021;76(2):428–55.
[80] Vupputuri S, Batuman V, Muntner P, et al. Effect of blood pressure on early decline in kidney function among hypertensive men. Hypertension 2003;42(6):1144–9.
[81] Akhtar M, Taha NM, Nauman A, et al. Diabetic kidney disease: past and present. Adv Anat Pathol 2020;27(2):87–97.
[82] Hsu CY, Ordoñez JD, Chertow GM, et al. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74(1):101–7.
[83] Otto M, Bucher C, Liu W, et al. 12(S)-HETE mediates diabetes-induced endothelial dysfunction by activating intracellular endothelial cell TRPV1. J Clin Invest 2020;130(9):4999–5010.
[84] Mennuni S, Rubattu S, Pierelli G, et al. Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. J Hum Hypertens 2014;28(2):74–9.
[85] Giustino G, Croft LB, Stefanini GG, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol 2020;76(18):2043–55.
[86] Tian J, Yuan X, Xiao J, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020;21(7):893–903.
[87] Shafi AMA, Shaikh SA, Shirke MM, et al. Cardiac manifestations in COVID-19 patients-A systematic review. J Card Surg 2020;35(8):1988–2008.
[88] Han H, Xie L, Liu R, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020;92(7):819–23.
[89] Qin J-J, Cheng X, Zhou F, et al. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. Hypertension 2020;76(4):1104–12.
[90] Danwang C, Endomba FT, Nkeck JR, et al. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 2020;8:37.
[91] Cosyns B, Lochy S, Luchian ML, et al. The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. Eur Heart J Cardiovasc Imaging 2020;21(7):709–14.
[92] Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17(9):1463–71.
[93] Doyen D, Moceri P, Ducreux D, et al. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet 2020;395(10235):1516.
[94] Elias P, Poterucha TJ, Jain SS, et al. The prognostic value of electrocardiogram at presentation to emergency department in patients with COVID-19. Mayo Clin Proc 2020;95(10):2099–109.
[95] Long B, Brady WJ, Bridwell RE, et al. Electrocardiographic manifestations of COVID-19. Am J Emerg Med 2021:41.
[96] Lancellotti P, Price S, Edvardsen T, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European association of cardiovascular imaging and the acute cardiovascular care association. Eur Heart J Acute Cardiovasc Care 2015;4(1):3–5.
[97] von Knobelsdorff-Brenkenhoff F, Schulz-Menger J. Role of cardiovascular magnetic resonance in the guidelines of the European Society of Cardiology. J Cardiovasc Magn Reson 2016;18:6.
[98] Lakkireddy DR, Chung MK, Gopinathannair R, et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the heart rhythm society COVID-19 task force; electrophysiology section of the American college of cardiology; and the electrocardiography and arrhythmias committee of the council on clinical cardiology, American heart association. Heart Rhythm 2020;17(9):e233–41.
[99] Chen D, Li X, Song Q, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in wenzhou, China. JAMA Netw Open 2020;3(6):e2011122.
[100] Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol 2020;75(18):2352–71.
[101] Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020;323(18):1824–36.
[102] Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5(9):1036–41.
[103] Bansal M. Cardiovascular disease and COVID-19. Diabetes Metabol Syndr 2020;14(3):247–50.
[104] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.
[105] Hua A, O'Gallagher K, Sado D, et al. Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19. Eur Heart J 2020;41(22):2130.
[106] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
[107] Bader F, Manla Y, Atallah B, et al. Heart failure and COVID-19. Heart Fail Rev 2021;26(1).
[108] Dawson DK. Acute stress-induced (takotsubo) cardiomyopathy. Heart 2018;104(2).
[109] Bapat A, Maan A, Heist EK. Stress-induced cardiomyopathy secondary to COVID-19. Case Rep Cardiol 2020;2020:8842150.
[110] Sang CJ, Heindl B, Von Mering G, et al. Stress-induced cardiomyopathy precipitated by COVID-19 and influenza A coinfection. JACC Case Rep 2020;2(9):1356–8.
[111] Lippi G, Favaloro EJ. D-Dimer is associated with severity of coronavirus disease 2019: a pooled analysis. Thromb Haemostasis 2020;120(5):876–8.
[112] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients

with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81.
[113] Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92(7):791–6.
[114] Darwish HS, Habash MY, Habash WY. COVID-19 viral pneumonia complicated with acute pulmonary embolism: a descriptive study. Radiol Res Pract 2021;2021:6649086.
[115] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950–73.
[116] Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemostasis 2020;18(8):1995–2002.
[117] Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemostasis 2020;18(5):1094–9.
[118] Viecca M, Radovanovic D, Forleo GB, et al. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020;158:104950.
[119] Zhu Y, Zhang J, Li Y, et al. Association between thrombocytopenia and 180-day prognosis of COVID-19 patients in intensive care units: a two-center observational study. PLoS One 2021;16(3):e0248671.
[120] Bagshaw SM, Langenberg C, Haase M, et al. Urinary biomarkers in septic acute kidney injury. Intensive Care Med 2007;33(7):1285–96.
[121] Fisher M, Neugarten J, Bellin E, et al. AKI in hospitalized patients with and without COVID-19: a comparison study. J Am Soc Nephrol 2020;31(9):2145–57.
[122] Pan X-W, Xu D, Zhang H, et al. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med 2020;46(6):1114–6.
[123] Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763–70.
[124] Pavenstädt H, Kriz W, Kretzler M. Cell biology of the glomerular podocyte. Physiol Rev 2003;83(1):253–307.
[125] Nagata M. Podocyte injury and its consequences. Kidney Int 2016;89(6):1221–30.
[126] Moreno JA, Sevillano Á, Gutiérrez E, et al. Glomerular hematuria: cause or consequence of renal inflammation? Int J Mol Sci 2019;20(9):2205.
[127] Maixnerova D, Jancova E, Skibova J, et al. Nationwide biopsy survey of renal diseases in the Czech Republic during the years 1994-2011. J Nephrol 2015;28(1):39–49.
[128] Yuste C, Rivera F, Moreno JA, et al. Haematuria on the Spanish registry of glomerulonephritis. Sci Rep 2016;6:19732.
[129] Lechner SM, Abbad L, Boedec E, et al. IgA1 protease treatment reverses mesangial deposits and hematuria in a model of IgA nephropathy. J Am Soc Nephrol 2016;27(9):2622–9.
[130] Yokote S, Ueda H, Shimizu A, et al. IgA nephropathy with glomerular capillary IgA deposition following SARS-CoV-2 mRNA vaccination: a report of three cases. CEN case reports 2022:1–7.
[131] Kanamori H. Gross hematuria can be an impact of severe acute respiratory syndrome coronavirus 2 vaccination on immunoglobulin A nephropathy: a case report. J Med Case Rep 2022;16(1):273.
[132] Bjornsson TD. Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 1979;4(3):200–22.
[133] Krstic D, Tomic N, Radosavljevic B, et al. Biochemical markers of renal function. Curr Med Chem 2016;23(19):2018–40.
[134] Bielecka-Dabrowa A, Mikhailidis DP, Jones L, et al. The meaning of hypokalemia in heart failure. Int J Cardiol 2012;158(1):12–7.
[135] Gabarre P, Dumas G, Dupont T, et al. Acute kidney injury in critically ill patients with COVID-19. Intensive Care Med 2020;46(7):1339–48.
[136] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 - final report. N Engl J Med 2020;383(19):1813–26.
[137] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–78.
[138] Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe covid-19. N Engl J Med 2020;382(24):2327–36.
[139] Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26(5):681–7.
[140] Nishiga M, Wang DW, Han Y, et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol 2020;17(9):543–58.
[141] Panel C-TG. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health; 2022 [Available from: https://www.covid19treatmentguidelines.nih.gov/.
[142] Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. Lancet Respir Med 2022.
[143] Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020;382(19):1787–99.
[144] Gautret P, Lagier J-C, Honoré S, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial revisited. Int J Antimicrob Agents 2021;57(1):106243.
[145] Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. Sci China Life Sci 2020;63(10):1515–21.
[146] Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. N Engl J Med 2020;382(25):2411–8.
[147] Singh B, Ryan H, Kredo T, et al. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev 2021;2(2):Cd013587.
[148] Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020;116(6):1097–100.
[149] Chang W-T, Toh HS, Liao C-T, et al. Cardiac involvement of COVID-19: a comprehensive review. Am J Med Sci 2021;361(1):14–22.
[150] Zhang P, Zhu L, Cai J, et al. 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;126(12):1671–81.
[151] Mancia G, Rea F, Ludergnani M, et al. Renin-angiotensin-aldosterone system blockers and the risk of covid-19. N Engl J Med 2020;382(25):2431–40.
[152] Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA statement addresses concerns Re: using RAAS antagonists in COVID-19. J Card Fail 2020;26(5):370.
[153] Soy M, Keser G, Atagündüz P, et al. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39(7):2085–94.
[154] Clavé S, Rousset-Rouvière C, Daniel L, et al. The invisible threat of non-steroidal anti-inflammatory drugs for kidneys. Front Pediatr 2019;7:520.
[155] Wen Y-C, Hsiao F-Y, Chan KA, et al. Acute respiratory infection and use of nonsteroidal anti-inflammatory drugs on risk of acute myocardial infarction: a nationwide case-crossover study. J Infect Dis 2017;215(4):503–9.
[156] Little P. Non-steroidal anti-inflammatory drugs and covid-19. BMJ 2020;368:m1185.
[157] Alexander J, Tinkov A, Strand TA, et al. Early nutritional interventions with zinc, selenium and vitamin D for raising anti-viral resistance against progressive COVID-19. Nutrients 2020;12(8).
[158] Zhang J, Rao X, Li Y, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 2021;11(1):5.
[159] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–5.
[160] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4.
[161] Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents 2020;55(6):105982.
[162] Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with covid-19. N Engl J Med 2021;384(8):693–704.
[163] Rojas M, Rodríguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: possible mechanisms of action. Autoimmun Rev 2020;19(7):102554.
[164] Liu B, Li M, Zhou Z, et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun 2020;111:102452.
[165] Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med 2020;8(5):518–26.
[166] Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141(23):1930–6.
[167] Yang X, Cai S, Luo Y, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019-induced acute respiratory distress syndrome: a multicenter descriptive study. Crit Care Med 2020;48(9).
[168] Kang Y, Chen T, Mui D, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart 2020;106(15):1132–41.
[169] Azam TU, Shadid HR, Blakely P, et al. Soluble urokinase receptor (SuPAR) in COVID-19-related AKI. J Am Soc Nephrol 2020;31(11):2725–35.
[170] Lim ZJ, Ponnapa Reddy M, Curtis JR, et al. A systematic review of the incidence and outcomes of in-hospital cardiac arrests in patients with coronavirus disease 2019. Crit Care Med 2021;49(6):901–11.
[171] Supady A, DellaVolpe J, Taccone FS, et al. Outcome prediction in patients with severe COVID-19 requiring extracorporeal membrane oxygenation-A retrospective international multicenter study. Membranes 2021;11(3).
[172] Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol 2020;31(6):1157–65.
[173] Ng JH, Hirsch JS, Hazzan A, et al. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. Am J Kidney Dis : the official journal of the National Kidney Foundation 2021;77(2):204–15. e1.
[174] Gupta S, Coca SG, Chan L, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. J Am Soc Nephrol 2021;32(1):161–76.
[175] Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol 2021;32(1):151–60.