Kidney involvement in coronavirus-associated diseases (Review)

ZHICAI FENG[1], YUQING CHEN[2], YUQIN WU[3], JIANWEN WANG[1], HAO ZHANG[1] and WEI ZHANG[1]

[1]Department of Nephrology, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013; [2]The Graduate School of Fujian Medical University, Fuzhou, Fujian 350108; [3]Department of Radiology, The First Hospital of Changsha, Changsha, Hunan 410011, P.R. China

Received June 15, 2020; Accepted January 5, 2021

DOI: 10.3892/etm.2021.9792

Abstract. Since 2003, coronaviruses have caused multiple global pandemic diseases, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and coronavirus disease 2019 (COVID-19). Clinical and autopsy findings suggest that the occurrence of kidney injury during infection may negatively affect the clinical outcomes of infected patients. The authoritative model predicts that outbreaks of other novel coronavirus pneumonias will continue to threaten human health in the future. The aim of the present systematic review was to summarize the basic knowledge of coronavirus, coronavirus infection-associated kidney injury and the corresponding therapies, in order to provide new insights for clinicians to better understand the kidney involvement of coronavirus so that more effective therapeutic strategies can be employed against coronavirus infection in the future.

Contents

Correspondence to: Dr Wei Zhang or Professor Hao Zhang, Department of Nephrology, The Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha, Hunan 410013, P.R. China
E-mail: weizhangxy@126.com
E-mail: zhanghaoliaoqing@163.com

Key words: coronavirus, kidney injury, severe acute respiratory syndrome, Middle East respiratory syndrome, coronavirus disease 2019

1. Introduction

Coronavirus pneumonia is a respiratory infectious disease caused by coronavirus infection. Since the severe acute respiratory syndrome coronavirus (SARS-CoV) spread and caused infection globally in 2003, coronaviruses have gradually attracted public attention and have caused several serious epidemics (1-3).

Coronaviruses are a group of single-stranded positive-sense RNA viruses, of which 26 species are currently known (4,5). Based on their differences in antigen cross-reactivity and genetic composition, they are divided into 4 genera (α, β, γ and δ), of which only genera α and β contain strains that are pathogenic to humans (6-8). SARS-CoV-2 (the 2019 novel coronavirus), SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) belong to the β-coronavirus family (9,10). There are seven known coronaviruses that may cause human diseases, including HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV and MERS-CoV (11,12) and the newly discovered SARS-CoV-2 (13). These viruses may cause a variety of clinically critical conditions, including kidney injury. The aim of the present systematic review was to summarize the knowledge of coronavirus infection from the perspective of kidney injury.

2. SARS-CoV and kidney injury

SARS was first reported in Asia in early 2003, and similar diseases were subsequently reported in North America and Europe (14,15). Of a total of 8,422 patients diagnosed with SARS, 916 succumbed to the disease, bringing the case fatality rate to 10.87% (16). SARS-CoV was found to be the main pathogen of SARS based on the findings from a macaque infection model (17). SARS-associated coronavirus was the SARS pathogen identified from the *Macaca fascicularis* infection experiment (18). During the SARS-CoV infection, ~100% of adult and pediatric patients had fever, approximately half of all patients had cough and/or myalgia, and a small number of patients experienced upper respiratory symptoms (19,20). In 10-20% of the patients, blood urea nitrogen and urine creatinine levels were increased, indicating that SARS may directly or indirectly cause kidney injury (Table I) (21-26). Chu *et al* (21) reported that kidney involvement in SARS was significantly correlated with the severity of the disease, and that patients with chronic diseases were more likely to suffer from kidney

injury. Autopsy reports of some patients with SARS indicated local renal hemorrhage and varying degrees of acute tubular necrosis (27). *In situ* hybridization and electron microscopy indicated the presence of viral sequences and particles, respectively, in distal renal tubular epithelial cells (27-29). The presence of the virus in the distal tubules may explain the findings of viral RNA and isolation of SARS-CoV from urine samples (30-32).

3. MERS-CoV and kidney injury

The earliest reports of MERS can be traced back to June 2012, when MERS-CoV was isolated from a patient in Saudi Arabia who succumbed to severe respiratory disease (33). By December 2019, there were 868 reported deaths among 2,496 MERS cases worldwide, with a case fatality rate of 34.77% (16). Researchers indicated that MERS-CoV, the causative agent of the disease, may originate from bats (11), with dromedary as its intermediate host (34). The clinical manifestations in patients with MERS-CoV infection range from asymptomatic to severe infectious pneumonia, acute respiratory distress, septic shock and multiple organ failure leading to death (11). Approximately 40% of patients exhibited increased urine creatinine levels, suggesting that MERS-CoV may cause kidney injury in some patients (Table I) (35-37). *In vitro* infection experiments with primary human renal epithelial cells (PromoCell) revealed that MERS-CoV robustly replicated in culture and produced more infectious virions (38). Poissy *et al* (39) reported that the virus could be detected in the blood and the urine of their most severely ill patients with MERS-CoV infection. Patients with MERS-CoV infection usually manifested with early and rapid-onset acute renal failure, which adversely affected the disease progression (38-41). Alsaad *et al* (42) indicated that, in patients with MERS-CoV infection, the kidney displayed the characteristics of renal tubular epithelial cell degeneration and regeneration/acute kidney injury (AKI). Ng *et al* (43) found that, in patients with MERS-CoV infection, the kidney exhibited an increase in global sclerosing glomeruli, affecting 5-10% of the total glomeruli; thickening Bowman capsules; severe atherosclerosis and hyaline arteriolosclerosis; patchy interstitial inflammation; and intratubular proteinaceous and granular casts.

4. SARS-CoV-2 and kidney injury

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus (44,45). The pathogen of this disease, SARS-CoV-2, shows 75-80% similarity to the nucleotide sequence of SARS-CoV (45-47). The bat is presumed to be its animal host and an intermediate host (48-50). Although the main target organ of SARS-CoV-2 is the lung, several studies have demonstrated that SARS-CoV-2 may also induce kidney injury; 5-30% of patients exhibit increase blood urea nitrogen and urine creatinine levels and kidney injury, indicating that the kidney is also targeted by SARS-CoV-2 (Table I) (13,51-56). During the current COVID-19 pandemic, 4-7% of patients infected with SARS-CoV-2 developed AKI, and the AKI incidence may be even higher among patients with severe symptoms admitted to the intensive care unit (ICU) (51). Huang *et al* (54) analyzed 41 patients with SARS-CoV-2 infection and found that >10% had elevated creatinine levels. Among patients treated in the ICU, 23% had AKI. Patients with kidney injury (including increased creatinine and urea nitrogen, proteinuria, hematuria and AKI) were more likely to die in the hospital in a study of 710 patients with COVID-19. Cox regression analysis confirmed that kidney injury is one of the independent risk factors for poor prognosis (57). Su *et al* analyzed renal pathologies in 26 autopsies of patients with COVID-19 and found prominent acute proximal tubular injury, peritubular erythrocyte aggregation and glomerular fibrin thrombi with ischemic collapse (58). In another study, 251 of 333 patients (75.4%) presented with renal complications, including proteinuria, hematuria and AKI. Although renal complications often resolved within 3 weeks after the onset of symptoms, renal complications in COVID-19 were associated with higher mortality (59).

5. Comparison of kidney injury among SARS-CoV, MERS-CoV and SARS-CoV-2

Previous studies have reported that patients infected with SARS-CoV, MERS-CoV or SARS-CoV-2 may present with AKI, but the incidence across studies was not consistent. AKI was reported to develop in 5-15% cases of SARS and MERS-CoV infections, whereas early reports suggested a lower incidence of AKI among patients with COVID-19 infection (13,51). Chen *et al* (60) found that the mortality rate of AKI was highest in SARS (86.6%), followed by COVID-19 (76.5%) and MERS (68.5%). Autopsy results in patients with SARS-CoV infection revealed that the kidney exhibited local hemorrhage and different degrees of acute tubular necrosis instead of glomerular lesions (21,27). Unlike SARS, a MERS autopsy report revealed that the kidney had the characteristic of epithelial cell degeneration and regeneration, but the size and shape of the glomeruli were normal, with only minor ischemic changes (42). Su *et al* (58) analyzed renal pathologies in 26 autopsies of patients with COVID-19 and found prominent acute proximal tubular injury, peritubular erythrocyte aggregation and glomerular fibrin thrombi with ischemic collapse. Ding *et al* (29) reported that SARS-CoV was detected in distal convoluted renal tubules. *In situ* hybridization and electron microscopy also indicated the presence of viral sequences and particles, respectively, in distal renal tubular epithelial cells (27-29). MERS-CoV particles were localized in renal proximal tubular epithelial cells (42). SARS-CoV-2 particles were identified by electron microscopy in the cytoplasm of renal proximal tubular epithelial cells and podocytes, but less so in the distal tubules (58). Interestingly, all three coronaviruses were isolated from urine samples (30-32,61,62).

6. Possible mechanism of coronavirus-associated kidney injury

Kidney injury in coronavirus infection is mainly due to the ability of coronavirus proteins to bind to specific cell surface receptors (63-65). To date, two major functional receptors for coronavirus have been identified:

Angiotensin-converting enzyme 2 (ACE2) is mainly expressed in the lung, kidney, heart and other tissues;

Table I. Kidney involvement in coronavirus infection.

	Blood urea nitrogen[a]		Creatinine[b]		
Study (Refs.)	Normal (value ± SD)	Increased [no./total (%)]	Normal (value ± SD)	Increased [no./total (%)]	Acute kidney injury [no./total (%)]
SARS					
Chu *et al* (21)	4.6±4.8	NA	93.5±48.7	NA	36/536 (6.7)
Lu *et al* (22)	NA	167/801 (20.9)	NA	89/801 (11.2)	NA
Lee *et al* (23)	6.3±7.2	NA	99.0±111.8	NA	NA
Hsu *et al* (24)	3.2±1.5	NA	65.4±12.4	NA	NA
Jang *et al* (25)	NA	NA	NA	6/29 (20.7)	NA
Cheng *et al* (26)	5.3±1.8	24/142 (16.9)	86.0±16.0	14/142 (9.9)	NA
MERS					
Sun *et al* (35)	NA	NA	89.9±28.3	NA	NA
AlGhamdi *et al* (36)	NA	NA	NA	21/51 (41.2)	NA
Sherbini *et al* (37)	14.2±2.1	NA	148.3±29.3	NA	NA
COVID-19					
Chen *et al* (13)	5.9±2.6	6/99 (6.1)	75.6±25.0	3/99 (3.0)	3/99 (3.0)
Wang *et al* (51)	4.4±1.4	NA	72.0±21.0	NA	5/138 (3.6)
Guan *et al* (52)	NA	NA	NA	12/752 (1.6)	6/1099 (0.5)
Yang *et al* (53)	NA	NA	76.3±27.4	NA	15/52 (28.8)
Huang *et al* (54)	NA	NA	74.2±19.5	4/41 (9.8)	3/41 (7.3)
Xu *et al* (55)	NA	NA	NA	3/62 (4.8)	NA
Cai *et al* (56)	4.0±0.9	NA	63.0±13.4	NA	17/298 (5.7)
Su *et al* (58)	16.1±2.7	NA	99.7±16.2	NA	NA
Pei *et al* (59)	4.3±1.2	NA	70.0±13.5	NA	35/333 (10.5)

[a]Normal range, 3.6-9.5 mmol/l. [b]Normal range, 57.0-111.0 μmol/l. SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19, coronavirus disease 2019; NA, not available.

in the kidney, this protein is prominently expressed in the proximal tubule and at a lower level in the glomeruli (66,67). Dipeptidyl peptidase 4 (DPP4; also referred to as CD26) is also highly expressed in the kidney, small intestine and lung (68-70). DPP4 is also one of the renal tubular brush border membrane proteins and is present in glomerular podocytes and capillaries (71). The expression levels of ACE2 and DPP4 in normal tissues were examined by searching two public databases, A Database of Hepatocellular Carcinoma Expression Atlas (http://lifeome.net/database/hccdb/home.html) (72) and the Human Protein Atlas (HPA; https://www.proteinatlas.org/) (73,74). At the RNA level, the expression level of ACE2 in kidney tissues was higher compared with that in lung tissues (Fig. 1A and C), which is consistent with previous reports by Xu *et al* (75) and Hoffmann *et al* (76). The DPP4 expression in the kidney was also higher compared with that in the lung (Fig. 1B and D). ACE2 was abundantly expressed in the kidney (77), mainly in the brush border of the proximal tubule (65,78), which was consistent with immunohistochemistry results in the HPA (Fig. 1E). Pala *et al* (79) found that DPP4 was abundantly expressed in human glomerular endothelial cells, which was also consistent with the immunohistochemistry results in the HPA (Fig. 1E).

ACE2 is a functional receptor for SARS-CoV (80,81). Li *et al* (67) isolated the ACE2 protein from African green monkey (*Chlorocebus sabaeus*) kidney cells (VERO E6) infected with SARS-CoV, showing that ACE2 could efficiently bind to the S protein for the SARS-CoV. SARS-CoV efficiently replicated in 293T cells transfected with ACE2; however, when anti-ACE2 antibodies were added to the culture media, SARS-CoV was unable to replicate in 293T cells transfected with ACE2 (82). Batlle *et al* (83) found that only a few cell lines could be naturally infected by SARS-CoV, but when they were modified to express ACE2, the virus could infect and replicate in other cells. ACE2 expression is associated with virus titer. Yang *et al* (84) found that high ACE2 expression resulted in more serious SARS-CoV infection in mice. Analogous to other virus-receptor interactions, SARS-CoV spike protein binding to ACE2 in cell lines or SARS-CoV infections *in vivo* resulted in reduced ACE2 protein expression and aggravated lung injury (80). Both SARS-CoV RNA and viral particles were observed in kidney tubules in SARS autopsy specimens (27), indicating direct infection and replication in the kidney. These observations support that ACE2 is a functional receptor for SARS-CoV that can bind to the SARS-CoV S protein and undergo membrane fusion.

SARS-CoV-2 and SARS-CoV exhibited high homology (up to 79%) on bioinformatics analysis (50). The affinity

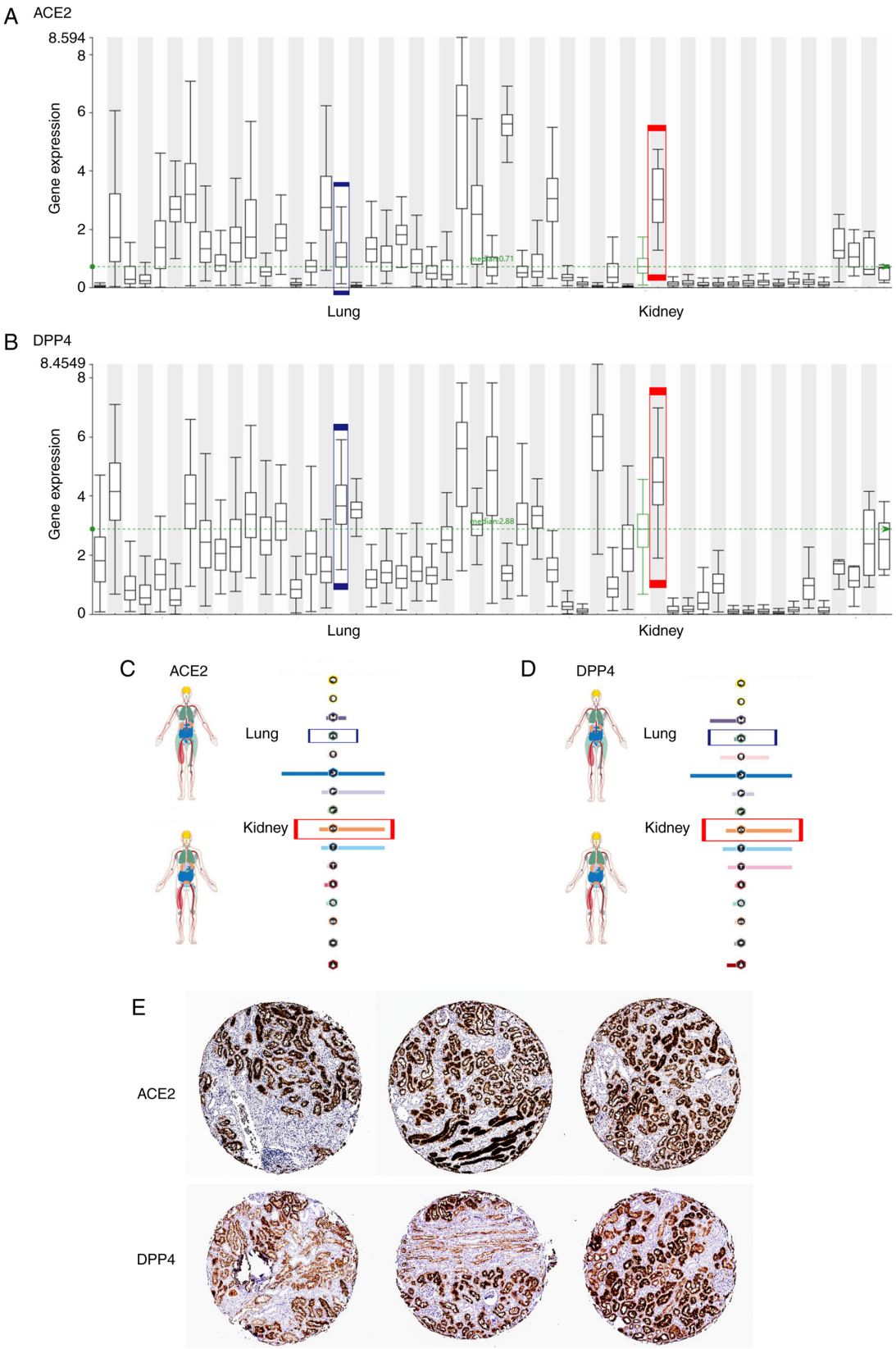

Figure 1. Analysis of ACE2 and DPP4 expression in different normal tissues using two databases. (A) ACE2 and (B) DPP4 expression data from A Database of Hepatocellular Carcinoma Expression Atlas. (C-D) ACE2 and DPP4 expression data from the Human Protein Atlas. (E) The ACE2 and DPP4 expression in kidney derived from the Human Protein Atlas (data was from antibody-based protein profiling using immunohistochemistry). Red box, kidney tissue; blue box, lung tissue. ACE2, angiotensin-converting enzyme 2; DPP4, dipeptidyl peptidase 4.

of SARS-CoV-2 was markedly higher compared with that of SARS-CoV when the S protein bound to the human ACE2 (85). SARS-CoV-2 can use ACE2 to enter the recipient cells and activate the S protein by the serine protease

TMPRSS2 on the host cell surface (76). Two studies that recently published online investigated the mechanism of how SARS-CoV-2 identifies and binds to human ACE2 and the composite crystal structure, which enhanced our understanding of the ACE2-mediated SARS-CoV-2 recognition and cell infection processes (86,87). Pan *et al* (88) concluded that the cytopathic effects of SARS-CoV-2 on podocytes and proximal straight tubule cells may cause AKI in patients with COVID-19, particularly those with evidence of SARS-CoV-2 infection in blood samples. Electron microscopic examination revealed that coronavirus particles were present in podocytes and renal tubular epithelial cells. In addition, immunostaining with SARS-CoV nucleoprotein antibody was positive in the tubules (58). SARS-CoV-2 nucleocapsid protein was detected in the renal tubular structure, and nucleocapsid protein-positive inclusion bodies were also observed in the renal cell cytoplasm (58). Researchers reported the presence of particles on the renal tubular epithelium, which were morphologically identical to SARS-CoV-2, and with viral arrays and other features of virus assembly, which constituted evidence of direct infection of the kidney by SARS-CoV-2. This finding confirmed that direct renal infection occurs in the setting of AKI in COVID-19 (89). Patients infected with SARS-CoV and SARS-CoV-2 developed kidney injury that may be caused by a direct attack on kidney cells through ACE2. It remains unclear how the virus causes AKI after infecting the kidney cells.

DPP4 is considered to be a functional receptor for MERS-CoV (68-70). MERS-CoV causes renal dysfunction by infecting epithelial cells (90). Raj *et al* (68) found that DPP4 specifically copurified with the receptor-binding S1 domain of the MERS-CoV spike protein from lysates of susceptible Huh-7 cells. Antibodies directed against DPP4 can inhibit MERS-CoV infection of primary human bronchial epithelial cells and Huh-7 cells (68). Expression of human and bat DPP4 in non-susceptible COS-7 cells enabled infection by MERS-CoV (68). These works identified DPP4 as a functional receptor for MERS-CoV. Chinese researchers demonstrated that the MERS-CoV receptor-binding domain was composed of a core subregion and an external receptor-binding subregion. The core subdomain is highly homologous to the SARS-CoV spike molecule, but the external subdomain is highly variable (91). It is conceivable that DPP4 may be the receptor through which MERS-CoV infects renal cells and causes kidney injury.

In addition, immune activation caused by viral infection may release a large amount of inflammatory mediators (such as IL-1, IL-6 and TNF), resulting in kidney injury (92,93). During the SARS outbreak, some critically ill patients experienced an inflammatory storm characterized by elevated IL-1β, IL-6, IL-12, IFN-γ, IP10 and MCP-1 levels (94). The 'cytokine storm' caused by MERS coronavirus is primarily associated with IFN-γ, TNF-α, IL-15 and IL-17 (95). SARS and MERS both induce a 'cytokine storm' in critically ill patients (96-98). COVID-19 patients may be affected by both the cytopathic effects directly induced by the virus as well as the systemic inflammatory responses caused by the cytokine storm, which may result in pathological changes in renal podocytes and proximal tubular cells and lead to AKI (88). Researchers analyzed the clinical characteristics of COVID-19 patients and found that, in patients with pneumonia, particularly in severe cases, there was a significant decrease in the lymphocyte count, and that a number of inflammatory factors (such as IL-6 and TNF) were increased significantly and that these may have caused kidney and other organ failure (51,54,99). Researchers also indicated that the virus may enter the blood circulation after lung infection, accumulate in the kidneys and cause kidney damage (100). Patients with viral infections suffered from anorexia, diarrhea and excessive perspiration, which may lead to hypovolemia and renal hypoperfusion, eventually causing kidney injury (101). Notably, certain antibiotics and antiviral drugs are also likely to cause drug-related kidney injury (102,103).

7. Coronavirus and blood purification

In addition to antiviral therapy and respiratory support, blood purification is also an important modality for treating coronavirus infections. According to the Kidney Diseases Improving Global Outcomes AKI guidelines, when continuous renal replacement therapy (CRRT) is used to treat COVID-19 patients, the therapeutic dose is 20-25 ml/kg/h post-dilution and 25-30 ml/kg/h predilution (104). Clinical studies demonstrated that the AKI incidence in COVID-19 patients was 3-7%, and the proportion of patients on CRRT was 1.5-9.0%; the AKI incidence in severe and critically ill patients admitted to the ICU was significantly increased, ranging from 8.3 to 23.0%, and CRRT was required for 5.6-23.0% of the patients, whereas CRRT was required for 66.7-100% of patients with AKI (13,51,54). It was previously demonstrated that 6.7-11.1% of patients with SARS developed AKI and 1.8% received CRRT (21). The incidence of AKI in MERS was 26.7 and 13.5-20% patients with AKI received CRRT (41,96). Up to 50% of MERS patients received CRRT (105). In addition, extracorporeal membrane oxygenation combined with CRRT was reported to effectively improve the patient's volume load and prognosis (106,107). However, it is worth noting that patients receiving maintenance hemodialysis are susceptible to COVID-19 and that hemodialysis centers are high-risk settings for COVID-19 (108).

CRRT eliminates the overexpressed inflammatory factors and anti-inflammatory transmitters in the blood circulation non-selectively, reducing the peak concentrations of these factors and downregulating the body's inflammatory responses (109). Plasma replacement, adsorption, perfusion and other special blood purification treatment technologies are mainly used in the early and middle stages of cytokine storms in severe and critically ill patients with COVID-19, mainly to block disease progression by reducing IL-6 levels (110,111). In addition to using antibodies against inflammatory factors, such as tocilizumab, to combat the cytokine storm (112,113), blood purification treatment may also effectively suppress the cytokine storm and reduce the mortality rate of patients with severe COVID-19 (110,114,115). However, according to a recent research, tocilizumab was not effective in preventing intubation or death in moderately ill hospitalized patients with COVID-19 (116). A benefit of dexamethasone was demonstrated in hospitalized patients with COVID-19 who were

treated with either invasive mechanical ventilation or oxygen alone (117).

In summary, blood purification is a key therapeutic strategy against COVID-19, particularly in critically ill patients with or without renal failure, and it may improve the prognosis and outcome of these patients.

8. Conclusion

Kidney injury is an important clinical issue in coronavirus infection. The two currently identified receptors for coronavirus infection, ACE2 and DPP4, may be the key mediators triggering direct kidney injury by the coronavirus, while it remains unclear how the coronavirus causes kidney injury after entering renal cells. ACE2 and DPP4 are potential therapeutic targets, and target drugs are developed based on their structure to block virus invasion before injury occurs. Therefore, it is necessary to carry out further basic and clinical research to guide clinical practice. Blood purification is an important treatment measure in coronavirus infection with or without kidney injury. Early and timely blood purification therapy may reduce or prevent disease progression in patients with coronavirus infection.

The current COVID-19 epidemic is still not under control globally. Although the vaccine is currently used on patients, it is still necessary to focus on infection prevention in patients with kidney disease, study the pathogenic mechanism of COVID-19 in depth, and optimize the treatment strategies for severely ill patients with AKI in order to improve their prognosis.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Sciences Foundation of China (grant nos. 81870498 and 81900633) and the National Natural Sciences Foundation of Hunan Province (grant no. 2017JJ2342).

Availability of data and materials

Not applicable.

Authors' contributions

ZF, HZ and WZ conceived and designed the study. YC, YW and JW contributed to drafted the manuscript and revised it critically for important intellectual content. ZF prepared the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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