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Review

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COVID-19 Pandemic Causing Acute Kidney Injury and Impact on Patients With Chronic Kidney Disease and Renal Transplantation

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Abstract

Coronavirus disease 2019 (COVID-19) caused by 2019 novel coronavirus (2019-nCoV) has caused significant mortality and has been declared as a global pandemic by the World Health Organization. The infection mainly presents as fever, cough, and breathing difficulty, and few patients develop very severe symptoms. The purpose of this review is to analyze the impact of the virus on the kidney. COVID-19 infection causes acute kidney injury (AKI) and is an independent risk factor for mortality. Angiotensin-converting enzyme 2 (ACE2) receptors, direct viral damage, and immune-mediated damage play important roles in the pathogenesis. AKI in COVID-19 infection could be from the synergistic effect of virus-induced direct cytotropic effect and cytokine-induced systemic inflammatory response. AKI caused in the viral infection has been analyzed from the available epidemiological studies. The proportion of patients developing AKI is significantly higher when they develop severe disease. Continuous renal replacement therapy (CRRT) is the most used blood purification technique when needed. The impact of COVID-19 infection on chronic kidney disease (CKD) and renal transplant patients is also discussed in the manuscript. No vaccine has been developed against the 2019-nCoV virus to date. The critical aspect of management is supportive care. Several investigative drugs have been studied, drugs approved for other indications have been used, and several clinical trials are underway across the globe. Recently remdesivir has received emergency use authorization by the Food and Drug Administration (FDA) in the USA for use in patients hospitalized with COVID-19. Prevention of the infection holds the key to management. The patients with underlying kidney problems and renal transplant patients are vulnerable to developing COVID-19 infection.

Keywords: COVID-19; Acute kidney injury; Chronic kidney disease; Renal transplant

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Introduction

A series of pneumonia cases from unexplained etiology in Wuhan, China, since December 2019 has created the public health concern and resulted in the identification of the viral cause. The initial reports of this viral infection were traced to the Huanan seafood market, Wuhan, China, and the etiological agent was identified as coronavirus [1]. The World Health Organization (WHO) has named the virus as 2019 novel coronavirus (2019-nCoV) on January 12, 2020 and has declared as public health emergency globally on January 30, 2020 [2]. The disease caused by the virus was named as coronavirus disease 2019 (COVID-19) on February 11, 2020 [3]. The International Committee on Taxonomy of Viruses designated the etiological coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. The number of cases has been multiplying at an alarming rate globally, resulting in mortality, and WHO has declared COVID-19 as pandemic on March 11, 2020 [5]. On May 2, 2020, there were 3.4 million confirmed cases of COVID-19 infection cases globally, and the number of reported deaths were 244,213 [6].

After SARS and Middle Eastern respiratory syndrome (MERS), COVID-19 is the third known zoonotic CoV infection, and all belong to the beta-CoV cluster [1]. There was no determination on the animal species carrying the nCoV. The preliminary studies showed that the nCoV is closely related to

the coronavirus isolated from bats, postulating the theory of possible transmission from bats to humans [1]. The genome homology sequence of SARS-nCoV and SARS-CoV was 79.5%, and SARS-nCoV had high homology with bat CoV [7]. All the studies suggest the evidence strongly that the SARS-nCoV might have originated from the bats, the intermediate host in transmission to humans yet to be ascertained. Ji et al have found that snakes are the wildlife repositories for the SARS-nCoV [8].

Various studies have reported the epidemiological data on SARS-nCoV. Most of the studies have shown that elderly patients are affected, higher male preponderance, and mortality is higher in the elderly with severe comorbid conditions [9]. The case fatality rate was estimated at 14-15%, depending on the case series described [9, 10]. The median incubation period is 14 days, and the median time from the first symptom to death is less in the elderly [1]. Mode of transmission is through close contact with people who has an infection through respiratory droplets when the infected person coughs or sneezes. Another possible mechanism is through infected surfaces and objects.

COVID-19 Infection and Incidence of Renal Failure

Epidemiological data revealed the severe illness rate of COVID-19 infection is as high as 25%, and even though the lungs are the main organs affected, the kidney is also one of the main organs affected in severe illness [11]. Acute kidney injury (AKI) was seen in 5-15% of the cases infected with SARS-CoV and MERS-CoV, and had a higher mortality rate of 60-90% as per the literature [12]. COVID-19 infection causes AKI and is an independent risk factor for mortality [13, 14]. It also impacts patients with chronic kidney disease (CKD), patients on chronic replacement therapies, and patients with a kidney transplant. Mohamed et al [15] evaluated the contributing factors for developing AKI in 161 intensive care unit (ICU) patients. In this study incidence of AKI was 28%. Approximately 35% of the patients who developed AKI had a history of CKD stages 3 - 5. Twenty-eight percent of the patients with CKD stages 3 - 5 had no AKI [15].

Pathogenesis

After the SARS-CoV2 spike (S) protein attaches to angiotensin-converting enzyme 2 (ACE2) receptors, the S protein is cleaved and activated by transmembrane serine proteases family (TMPRSS), which allows the virus to release fusion peptide that aids in the membrane fusion [16].

Mechanism

AKI in COVID-19 infection could be from the synergistic effect of virus-induced direct cytotropic effect and cytokine-induced systemic inflammatory response. AKI is more pronounced in patients with severe disease, acute respiratory distress syndrome (ARDS), and those needing ICU admission. Other possible mechanisms of AKI could be from acute tubular necrosis (ATN) due to multiorgan failure and shock, and possible prerenal etiology from volume depletion secondary to decreased oral intake and high fever. Drug toxicity, hemodynamic insult, and contrast exposure can also play a role. The workup for AKI in COVID-19 infection should be similar to the other causes of AKI. Mohamed et al [15] discussed different etiologies of AKI in their study which include ischemic acute tubular injury, toxic acute tubular injury or combination of both, acute interstitial nephritis, *de novo* glomerular disease, pre-renal azotemia, and unspecified reasons. The contributing factors to different etiologies include hypotension, shock, rapid atrial fibrillation, prolonged volume depletion, rhabdomyolysis, toxic agents such as vancomycin, and iodinated contrast, overt proteinuria [15].

Direct viral damage

Prior studies have shown that positive SARS-CoV ribonucleic acid (RNA) polymerase gene fragments were detected by immunohistochemistry and *in situ* hybridization in kidney specimens of autopsy patients died from SARS [17]. MERS-CoV infections also have been shown to cause kidney epithelial cell damage by apoptosis mediated through receptors [18]. These studies suggest that the injury from coronavirus is a direct cytotoxic effect on kidney epithelial cells. Diao et al analyzed the kidney tissue in six patients on autopsy; immunohistochemistry demonstrated the presence of SARS-CoV-2 nucleocapsid (NP) protein in the kidney tubule, possibly related to potential direct tubular injury from the virus [19]. The SARS-CoV-2 RNA was detected in the urine of the patients by quantitative real-time polymerase chain reaction (qRT-PCR) [20].

Role of ACE2 receptors

The normal human lung has type 1 and type 2 alveolar epithelial cells, which express ACE2 and is expressed in 83% of type 2 cells. Men have a higher expression rate of ACE2 levels compared to women, and similarly, Asians express higher ACE2 levels compared to white and African American populations [1]. The analysis by Xu et al found that ACE2 receptor expression in the kidney is no less than the lung on comparative analysis [16]. Podocytes and proximal convoluted tubule cells significantly co-express *ACE2* and *TMPRSS* genes that are potential targets for SARS-CoV-2. The kidney tissue expresses the *ACE2* gene higher than that of lung tissue. The binding affinity of SARS-CoV-2 to ACE2 receptors is 10 - 20 times higher than SARS-CoV as described by Wrapp and colleagues [21].

Immune-mediated damage

The pro-inflammatory cytokine levels were elevated in COVID-19 infection and probable activation of T-cell response [9].

Table 1. Diagnosis of AKI Was Based on the KDIGO Classification

AKI staging	Serum creatinine	Urine output
Stage 1	Increase of more than or equal to 0.3 mg/dL (≥ 26.5 mmol/L) or increase to more than or equal to 150-200% (1.5- to 2-fold) from baseline	Less than 0.5 mL/kg/h for more than 6 h
Stage 2	Increased to more than 200-300% (2- to 3-fold) from baseline	Less than 0.5 mL/kg/h for more than 12 h
Stage 3	Increased to more than 300% (> 3-fold) from baseline, or more than or equal to 4.0 mg/dL (≥ 354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) or on RRT	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

AKI: acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; RRT: renal replacement therapy.

The possible occurrence of cytokine storm in severe cases is evidenced by the significantly higher cytokine levels. In the cytokine storm, the immune system damages healthy tissues rather than SARS-CoV-2 [16]. On the autopsies of six kidney tissues, the light microscopy revealed cluster of differentiation 68 ($CD68)^+$ macrophage infiltration of the tubulointerstitium and severe ATN. The tubules showed complement 5b-9 deposition in all six cases, but deposition in glomeruli and capillaries were seldom seen. Some $CD8^+$ T lymphocyte cells and $CD56^+$ (natural killer) cells were seen in kidney tissue [19].

COVID-19 Infection and AKI

Recently published studies in China showed that the incidence of AKI in patients infected with COVID-19 is around 3-15% [22, 23]. In patients with severe COVID-19 infection in ICU, the rates of AKI increased significantly to 14.5-50% [23, 24]. The variation in reporting the incidence of AKI depends on the number of patients, severity of infection, and reporting of AKI across the studies. The diagnosis of AKI based on kidney disease improving global outcomes (KDIGO) classification was summarized in Table 1 [25].

Cohort studies

Cheng and colleagues analyzed a large cohort of 710 patients for kidney disease with confirmed COVID-19 admitted to Tongji Hospital from January 28, 2020 to February 11, 2020 [22]. All the patients were above 18 years of age. Patients who have a history of renal transplant and on maintenance dialysis were excluded from the study. The baseline serum creatinine was elevated in 110 patients on admission.

The patients in the elevated serum creatinine group were elderly, had a higher percentage of males, and the days from onset of illness to hospital admission were shorter. These patients also had severe disease and co-morbidities compared to those with normal baseline serum creatinine. These patients had more pronounced AKI and higher rates of mechanical ventilation, and the hospital mortality rate was higher.

Patients with elevated serum creatinine also had leukocytosis, lymphopenia, thrombocytopenia, prolonged activated partial thromboplastin time, and higher D-dimer levels. The patients with elevated baseline serum creatinine had a higher percentage of increased procalcitonin, aspartate aminotransferase, and lactic dehydrogenase levels.

Most of the AKI occurred within 7 days, but was much quicker and severe in elevated baseline serum creatinine group. Patients with normal baseline creatinine had later onset of AKI and recovered quickly. There was elevated blood urea nitrogen (BUN), creatinine, high-grade proteinuria, and hematuria in elevated baseline serum creatinine patients along with significantly lower estimated glomerular filtration rate (eGFR). There was a significant gap between peak and baseline creatinine in the elevated serum creatinine group. Patients with elevated serum creatinine from baseline had worse outcomes compared to patients with normal baseline serum creatinine.

The study by Li et al [14] analyzed 59 cases of inpatients from multiple hospitals around Wuhan from January 21, 2020 to February 7, 2020 with COVID-19 disease, and 28 patients were diagnosed with severe cases according to the Chinese Nation Health guidance. Three of the patients died in the severe cases [14]. Proteinuria was present in 63% of the patients, and many of them had detected protein on the first day of admission, suggesting the presence of prior renal impairment. BUN was elevated in 27% of the patients, and an also higher level of BUN was present in two patients who died. Serum creatinine was elevated in 19% of the patients, and the patients who died had extremely high levels. The density was reduced on the computed tomography (CT) images of the kidney suggestive of edema and inflammation.

In a study by Wang et al [26], the patients needing ICU admission had higher BUN and creatinine levels at hospital admission compared to non-ICU admission patients and overall patients in general. The BUN and creatinine levels continued to get worse in non-survivors until the death [26].

We summarized the finding from multiple studies including patient characteristics, co-morbidities, incidence of AKI in general as well as ICU/severely ill patients, number of patients requiring continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO) and mortality in Table 2 [9-11, 13, 19, 22-24, 26-32].

Renal replacement therapies (RRTs) in hospital

In the patients who developed AKI from COVID-19 infection, around 1.5-9% of them required RRT in the form of CRRT [26, 28]. The proportion of patients needing RRT increased to 5.2-25% with severe infection [11, 27]. As per the international experts, in severe COVID-19 cases with hypoxemic respira-

Table 2. Summary of Findings From Multiple Studies Including Patient Characteristics, Comorbidities, Incidence of AKI in General as Well as ICU/Severely Ill Patients, Number of Patients Requiring CRRT, ECMO and Mortality

Study/country	Related information	N	Median age in years	Males	Comorbid conditions, N (%)	AKI, N (%)	AKI ICU admission or severe disease, N (%)	CRRT, N (%)	ECMO, N (%)	Mortality, N (%)
Wang et al, 2020 [26]/China		138	56	75 (54.3%)	HTN, 43 (31.2%) CVD, 20 (14.5%) DM, 14 (10.1%) CKD, 4 (2.9%)	5 (3.6%)	3 (8.3%)	2 (1.45%)/T 2 (5.5%)/I	4 (2.9%)/T 4 (11.1%)/I	6 (4.3%)
Guan et al, 2020 [27]/China		1,099	47	637 (58%)	HTN, 165 (15%) CVD, 27 (2.5%) DM, 81 (7.4%) CKD, 8 (0.7%)	6 (0.5%)	5 (2.9%)	9 (0.8%)/T 9 (5.2%)/S	5 (0.5%)/T 5 (2.9%)/S	15 (0.4%)/ T 14 (8.1%)/ S
Yang et al, 2020 [11]/China	Critically ill patients, 17 (33%) patients with Huanan sea market exposure	52	60	35 (67%)	HTN (NA) CVD, 2 (10%) DM, 2 (10%) CKD, NA	15 (29%)	15 (29%)	9 (17%)/T 8 (25%)/S	6 (11.5%)/T 5 (16%)/S	32 (61.5%)
Zhou et al, 2020 [23]/China		191	56	119 (62%)	HTN, 58 (30%) CVD, 15 (8%) DM, 36 (19%) CKD, 2 (1%)	28 (15%)	27 (50%)	10 (5%)/T 10 (19%)/S	3 (2%)/T 3 (6%)/S	54 (28.2%)
Huang et al, 2020 [9]/China	27 (66%) patients with Huanan sea market exposure. Among them 9 (69%) needed ICU care	41	49	30 (73%)	HTN, 6 (15%) CVD, 6 (15%) DM, 8 (20%) CKD (NA)	3 (7%)	3 (23%)	3 (7%)/T 3 (23%)/I	2 (5%)/T 2 (15%)/I	6 (15%)/ T 5 (38%)/ I
Chen et al, 2020 [28]/China	49 (49%) patients with Huanan sea market exposure	99	55	67 (68%)	HTN (NA) CVD, 40 (40%) DM, 12 (12%) CKD (NA)	3 (3%)	NA	9 (9%)	3 (3%)	11 (11%)
Wu et al, 2020 [10]/China		201	51	128 (63.7%)	HTN, 39 (19.4%) CVD, 8 (14%) DM, 22 (11%) CKD, 2 (1%)	9 (4.5%)	NA	NA	1 (0.5%)	44 (22%)
Cheng et al, 2020 [22]/China		710	63	374 (52.6%)	HTN (NA) CVD(NA) DM (NA)	22 (3.2%)	NA	NA	NA	89 (12.3%)

Table 2. Summary of Findings From Multiple Studies Including Patient Characteristics, Comorbidities, Incidence of AKI in General as Well as ICU/Severely Ill Patients, Number of Patients Requiring CRRT, ECMO and Mortality - *(continued)*

Study/country	Related information	N	Median age in years	Males	Comorbid conditions, N (%)	AKI, N (%)	AKI ICU admission or severe disease, N (%)	CRRT, N (%)	ECMO, N (%)	Mortality, N (%)
					CKD (NA)					
Cheng et al, 2020 [13]/China		701	63	367 (52.4%)	HTN, 233 (33.4%) CVD (NA) DM, 100 (14.3%) CKD, 14 (2%)	36 (5.1%)	NA	NA	NA	113 (16.1%)
Arentz et al, 2020 [29]/USA		21	70	11 (52%)	HTN (NA) CVD, 9 (42.9%) DM, 7 (33.3%) CKD, 10 (47.6%) ESRD, 2 (9.5%)	4 (19.1%)	4 (19.1%)	NA	NA	11 (52.4%)
Zhang et al, 2020 [24]/China		221	55	108 (48.9%)	HTN, 54 (24.4%) DM, 22 (10%) CVD, 22 (10%) CKD, 6 (2.7%)	10 (4.5%)	8 (14.5%)	5 (2.3%)/T 4 (7.3%)/S	10 (4.5%) 10 (18.2%)	12 (5.4%)
Diao et al,2020 [19]/China		85	67	48 (56%)	HTN, 17 (20%) DM, 7 (8%) CVD, 16 (18%) CKD, 5 (5.8%)	23 (27%)	NA	NA	NA	NA
Cao et al, 2020 [30]/China		199	58	120 (60.3%)	DM, 23 (11.6%) HTN (NA) CVD (NA) CKD (NA)	9 (4.5%)	NA	9 (4.5%)	4 (2%)	44 (22%)
Wan et al, 2020 [31]/China		135	47	72 (53.3%)	HTN, 13 (9.6%) CVD, 7 (5.2%) DM, 12 (8.9%) CKD (NA)	5 (3.7%)	1 (2.5%)	5 (3.7%)/T 4 (10%)/S	0	1 (0.7%)
Cao et al, 2020 [32]/China		198	50	101 (51%)	HTN, 42 (21.1%) CVD, 12 (6 %) DM, 15 (7.6%) CKD (NA)	10 (5.3%)	3 (15.8%)	NA	NA	NA

CRRT: continuous renal replacement therapy; ECMO: extra corporeal membrane oxygenation; N: number of patients; AKI: acute kidney injury; ICU: intensive care unit; HTN: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; CKD: chronic kidney disease; ESRD: end-stage renal disease; T: total patients; I: ICU patients; S: patients with severe disease; NA: not available.

tory failure along with renal or liver dysfunction, ECMO with or without CRRT, can be used. CRRT is the most used blood purification modality in clinical practice, but for severe COVID-19 patients with sepsis and ARDS, hemoperfusion/plasma adsorption treatment can also be selected to clear more inflammatory mediators [33].

Recommendations on the care of hospitalized patients with COVID-19 and kidney failure needing RRT from the American Society of Nephrology (ASN) was summarized below [34].

General measures

All the health care personnel should follow the Centers for Disease Control and Prevention (CDC)-recommended personal protective equipment (PPE) and safety guidelines during their interactions with the patients. All the health care personnel should work as a team to limit the exposure to the infection. Indications for RRT are similar to other patients with AKI, and providers with significant expertise should place dialysis catheters.

Patients in ICU

The patients should be cohorted in dedicated ICUs, if possible. The preferred dialysis modality is CRRT or slow, low-efficiency dialysis (SLED) if available. Intermittent hemodialysis (IHD) can also be performed if CRRT and SLED are not available. CRRT is preferred over IHD in the setting of isolation, as IHD needs one-on-one nursing support. The patients needing CRRT exceeds the machines available, prolonged intermittent treatments (e.g., 10 h instead of continuous) with higher flow rates (e.g., 40 - 50 mL/kg/h) and after terminal cleaning, can be used for another patient.

Patients in general hospital floors

The patients should be cohorted on the dedicated floor, if possible. Patients with active or suspected COVID-19 needing dialysis treatment should not be transported to a central acute dialysis unit. IHD should be provided with one-on-one nursing care if the patient is in negative pressure room. If all the COVID-19 patients are isolated on one floor, one dialysis nurse may be able to monitor two or three patients during IHD if video/electronic monitoring is available. The nurse enters the room if the patient needs anything or to troubleshoot the machine. The peritoneal dialysis can be continued as automated peritoneal dialysis (APD) to limit the exposure of medical staff.

Care and disinfection of RRT equipment

The dialysis equipment should be cleaned with the disinfectant before removing it from the room. Hospital infection control and policy directs the proper disposable of RRT machine equipment. As per the hospital protocol, CRRT filters need to be changed every 72 h or longer.

Continuous venovenous hemofiltration, also known as CVVH or continuous venovenous hemodiafiltration (CVVHDF) are the preferred techniques. In the USA, continuous venovenous hemodialysis (CVVHD) is the most common modality used. Volume overloaded patients can be treated using slow continuous ultra-filtration (SCUF) to keep fluid balance net negative [35].

Temporary dialysis catheters are recommended for the vascular access and the providers with significant expertise should place dialysis catheters. It is recommended to use double-layered protection for the personnel performing the procedure. Filters with high ultrafiltration coefficient and high molecular weight cut-off membrane with 8 - 10 nm membrane pore size are suggested [36]. This would help in clearing high molecular weight inflammatory mediators. However, albumin would need to be replaced as it can be removed concurrently. It is essential to assess the patient's bleeding risk before choosing anti-coagulation. Patients with severe COVID-19 infection having high bleeding risk, it is recommended to avoid anticoagulation. In normal or hypercoagulable states, one can use heparin or citrate-based anticoagulation depending on hospital protocols. When using CRRT in combination with ECMO, anticoagulation is not needed as ECMO utilizes systemic heparinization [35].

It is essential to pay a very close attention to hemodynamics and volume status of patients with COVID-19 infection by using arterial and central venous pressure (CVP) monitors. Patients should have frequent renal panels checks every 4 - 6 h and monitor strict input and output to maintain a net negative fluid balance in ARDS patients. In patients without ARDS, the volume status should be assessed to maintain in euvolemic state.

The patients should be monitored for recovery of kidney function on daily basis, and the RRT should be discontinued once the patient is non-oliguric, euvolemic and improved ventilation requirements. This should also be supported by improved laboratory findings without alarming electrolyte or acid-base imbalance.

Strategies to limit AKI

AKI was associated with increased in-hospital mortality, so the patient should be meticulously managed by providing hemodynamic support, avoiding non-steroidal anti-inflammatory drugs (NSAIDs), nephrotoxins, and contrast. Early institution of CRRT will improve the outcomes. Proteinuria and hematuria were also associated with in-hospital mortality, so close attention should be paid to urine analysis, both in-patient and out-patient settings.

AKI and mortality with COVID-19 infection

The experience from various published studies on patients infected with COVID-19 infection showed that AKI is associ-

ated with mortality. Shi et al analyzed 101 patients who died from COVID-19 infection showed that 23% had AKI and 11% of patient had underlying CKD. BUN and myoglogin levels were higher in patients who died within 3 days and median time from hospitalization to death is 4 days [37]. Cheng in his analysis showed that elevated baseline serum creatinine, elevated BUN, peak serum creatinine > 1.5, proteinuria, hematuria, AKI stages 2 and 3 are all associated with mortality after adjusting for confounding factors [22].

COVID-19 Infection and CKD

The impact of COVID-19 infection on CKD has not been reported. The incidence of known CKD patients varied from 0.7-47.6%, depending upon the series described [27, 29]. There was increased mortality in patients described in one study [29]. The incidence of AKI was higher in patients with established CKD [22].

The studies analyzed the kidney function in patients admitted with confirmed COVID-19 infection revealed the incidence of proteinuria and hematuria [14, 22]. A significant number of patients had proteinuria on the day of admission, which could be related to the cytotropic effects of the virus on the podocytes. Proteinuria may result from direct podocyte injury from an expression of ACE2 [16].

The patients who recovered from the COVID-19 infection with proteinuria and hematuria need to be followed closely for the resolution. The patients who have sustained AKI during the infection need to be monitored for CKD.

Renal Transplant and COVID Infection

The ongoing outbreak of COVID-19 has amassed great concern worldwide, but its influence on transplant recipients is unknown. Previously experienced coronavirus outbreaks have taught us that transplant recipients can be easily affected by these infections [38, 39]. With this being said, very little is known about the risk of the donor to receive transmission of the disease. Several factors concerning donor exposure like infectivity, incubation period, etc., can play an important role. Although there are no strict guidelines about donor restrictions, it would be advisable for potential donors to hold off on organ donation if suffering from a respiratory illness. The American Red Cross and European Centre for Disease Prevention and Control (ECDC) recommend 28-day and 21-day period delay respectively for potential organ donors with a history of recent travel to high-risk areas or contact with a person with suspected or proven COIVD-19 [40, 41]. The ECDC recommends a 28-day delay after recovery from a confirmed infection. Michaels and colleagues recently well described possible risks associated with transplants in COVID-19-positive recipients [42]. Andrea et al from Italy described in their experience that in their institution, they have been limiting liver transplantation to the most urgent cases for the residents in the epidemic area [43].

A more liberal allocation policy is used for patients outside epidemic areas. However, all recipients are screened to avoid transplantation in SARS-CoV-2-positive subjects. The internal board consistently reviews and updates the transplant list every 2 weeks according to the new insights on COVID-19. They continuously train their healthcare providers and screen them with nasopharyngeal swabs at frequent intervals. Providing timely information to patients and their caregivers to raise awareness and at the same time to avoid panic and confusion is important [43].

As per the review of the literature to the best of our knowledge, only one case of COVID-19 infection has been described in kidney transplant recipients of 12 years [44]. The patient was successfully managed initially with the cessation of all immunosuppression. He was given intravenous stress dose steroids to prevent adrenal insufficiency. Once the patient improved clinically, immunosuppression was resumed gradually. The overall clinical characteristics, including the symptoms, radiological findings on lung imaging, and laboratory findings, were similar to those of other non-transplanted adult patients with COVID-19 pneumonia. This being the only case reported so far, it is difficult to say that it is not possible to see atypical findings or more severe presentations of COVID-19 disease in transplant recipients.

Healthcare providers should be aware of that the experimental drugs like remdesivir and lopinavir/ritonavir could cause drug-drug interactions with calcineurin inhibitors [42]. It is therefore recommended to use these drugs with extreme caution. Regarding the treatment of kidney transplant recipients with COVID-19 infection, there is not much information available to help guide therapy and immunosuppression regimens. For now, it would be recommended to use due diligence and tailor management and treatment options based on the patient's clinical status, duration of transplant, and severity of illness. As the pandemic progresses, we now expect that we will have more information available for guidance.

Treatment

No vaccine has been developed against the SARS-CoV-2 virus to date. The critical aspect of management is supportive care. Multiple treatments such as empiric antibiotics, antiviral therapy, and systemic corticosteroids have been used worldwide. Several investigative drugs have been studied, drugs approved for other indications have been used, and several clinical trials are underway all across the globe.

One of the most promising of these therapies is remdesivir. It inhibits viral replication by premature termination of RNA transcription, and has shown activity against beta coronaviruses and *in vitro* activity against SARS-CoV-2 [45]. It has received emergency use authorization by the Food and Drug Administration (FDA) in the USA for use in patients hospitalized with COVID-19. It is recommended for 5 days in patients who are not on mechanical ventilation or ECMO, and recommended for 10 days in patients who are on mechanical ventilation or ECMO [46]. It is not recommended in patients with lower GFR (GFR < 30 mL/min) [47].

Others drug that has gained more attention was chloro-

quine, hydroxychloroquine either alone or in combination with azithromycin. Chloroquine and hydroxychloroquine both have *in vitro* activity against SARS-CoV-2 [45]. They are both used in several countries for treating COVID-19 infection based on anecdotal data and in-vitro studies. There was a news report from China, where chloroquine increased viral clearance, decreased disease progression, and improved radiological findings [47, 48]. There was another clinical trial reported from France, which is a non-randomized open-label trial of 36 patients compared to hydroxychloroquine or a combination of hydroxychloroquine and azithromycin versus standard of care in the control group. The combination of hydroxychloroquine and azithromycin in six patients resulted in superior viral clearance compared with hydroxychloroquine monotherapy [49]. There was a recent study among 368 veterans, which found no benefit of hydroxychloroquine but associated with more risks due to its side effect profile [50]. These medications should be used with caution in patients with renal and hepatic impairment, and they can cause QT prolongation in the electrocardiogram.

Hydroxychloroquine use for pre and post-exposure prophylaxis and treatment for SARS-CoV-2 infection is currently under investigation. Several clinical trials are planned in the USA to test the usage of hydroxychloroquine for treatment and prophylaxis for COVID-19. Clinicians are using different doses of hydroxychloroquine for prophylaxis and treatment.

A recent clinical trial in China did not show the efficacy of lopinavir-ritonavir for the treatment of pneumonia for COVID-19 patients, but this trial was underpowered [30]. WHO launched a global mega trial called SOLIDARITY of four most promising coronavirus treatments (remdesivir; chloroquine and hydroxychloroquine; ritonavir/lopinavir; ritonavir/lopinavir and interferon beta) [51].

When antiretroviral medications for coronavirus treatment are used like lopinavir and ritonavir, dose adjustments to medications during CRRT are not needed, as they are 90% protein bound. Particular attention should be paid to the dosing of the drugs.

Other drugs are interferon beta, interferon alpha, mefloquine, favipiravir, darunavir, ribavirin, umifenovir, tocilizumab, and type II transmembrane serine protease (TMSPSS2) inhibitors. Support to therapies using vitamin A, B, C, D, E, thymosin alpha 1, thymopentin, Selenium, zinc and pyrithione combination have been used for treatment against SARS-COV-2 infection [47, 52].

Conclusions

COVID-19 infection is spreading rapidly and causing mortality daily worldwide. Unfortunately, knowledge about the novel virus is limited, and it causes a significant clinical threat to the general population and healthcare workers. Several countries have imposed strict regulations on the public to limit the spread of the virus. Many government agencies like CDC, FDA, and hospitals, public health systems are working every day in the USA to contain the spread of infection.

Studies have shown that there is the involvement of kidneys with COVID-19 infection and can be associated with high mortality. Health care providers should recognize this aspect early, and appropriate management should be instituted as soon as possible. The patients with underlying kidney problems and renal transplant patients are vulnerable to developing COVID-19 infection.

There is limited understanding of the pathogenesis of the disease, virulence of the virus at this moment, so prevention is the critical aspect in the management. Several vaccines and promising treatments are undergoing clinical trials with the hope of finding a cure for this global crisis soon.

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Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

All authors contributed equally. SA, AC, MB, GPM, NMK, SRD, VG, SN, and VMK were involved in review, and preparation of the manuscript. SA and VMK were involved in the analysis of data, final review of the manuscript, preparation of tables as well as submission. All the authors reviewed the manuscript and agreed with the findings and interpretation.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

WHO: World Health Organization; 2019-nCoV: 2019 novel coronavirus; COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MERS: Middle Eastern respiratory syndrome; AKI: acute kidney injury; CKD: chronic kidney disease; ACE2: angiotensin-converting enzyme 2; TMPRSS: transmembrane serine proteases family; RNA: ribonucleic acid; qRT-PCR: quantitative real-time polymerase chain reaction; ICU: intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; ARDS: acute respiratory distress syndrome; ATN: acute tubular necrosis; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; CT: computed tomography; CRRT: continuous renal replacement therapy; ECMO: extracorporeal membrane

oxygenation; ASN: American Society of Nephrology; CDC: Centers for Disease Control and Prevention; PPE: personal protective equipment; SLED: slow low efficiency dialysis; IHD: intermittent hemodialysis; APD: automated peritoneal dialysis; CVVH: continuous venovenous hemofiltration; CVVHDF: continuous venovenous hemodiafiltration; CVVHD: continuous venovenous hemodialysis; SCUF: slow continuous ultra-filtration; CVP: central venous pressure; NSAIDS: non-steroidal anti-inflammatory drugs; ECDC: European Centers for Disease Prevention and Control

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