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Pharmacotherapy for Patients with Chronic Kidney Disease during the COVID-19: A Narrative Review

Mansour Adam Mahmoud[1*]

[1]Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Al-Madina Al-Munawarah, Saudi Arabia.

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: COVID-19 is considered the most challenging global pandemic. Patients with COVID-19 are more vulnerable to renal impairment especially those admitted to the Intensive Care Units (ICUs).
Objective: In this review we discuss the epidemiology, the pathophysiology, the clinical implications and specific COVID-19 therapy in CKD patients.
Results: The prevalence of CKD patients with COVID-19 varies between 0.7 to 47.6%. Patients with CKD ought to be encouraged to take extra precautions (isolation, distancing, wearing Personal Protective Equipment (PPE)) to limit the risk of exposure to the virus. Renin-Angiotensin System (RAS) and SARS-CoV-2 interactions, through the binding of the virus to ACE-2, have produced speculations of both likely damage and advantage of RAS inhibitor use during the pandemic. Remidisivir should be avoided in CKD patients (Cr Cl<30ml/min) with COVID-19. In addition, the doses of nephrotoxic medications (chloroquine phosphate and dexamethasone) that are recommended to be used in the management of COVID-19 should be adjusted according to creatinine clearance and dialysis.

**Corresponding author: E-mail: Mammm.99@gmail.com;*

Conclusion: COVID-19 may worsen the impaired kidney function and increase mortality. Care givers should pay especial attention to medications dosing in COVID-19 patient with CKD history.

Keywords: SARS-CoV-2; COVID-19; treatment; chronic kidney disease; nephrology.

1. INTRODUCTION

In December 2019, China reported the first corona virus case, produced by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which had spread all over the globe since December 2019 [1]. According to the World Health Organization (WHO) situation report (as reported by national authorities by 2:45pm CEST, 22 October 2020), a total of 41,104,946 confirmed cases of COVID-19 and 1,128,325 deaths are confirmed globally [2]. COVID-19 belongs to the same beta-corona viruses β-CoVs family as SARS-CoV and MERS-CoV, which broke out in 2003 and 2015, respectively [3]. The morbidity and mortality of SARS-CoV-2 are more prevalent in older subjects with existing comorbidities [4]. Furthermore, cases having chronic kidney disease (CKD) have often manifested multiple comorbidities, including hypertension, diabetes, and cardiovascular illnesses. CKD is a public health concern that accounted for around 850 million patients around the world, and the sixteenth driving reason for years of life lost (YLL) [5]. Clinical features of COVID-19 disease can differ from minor self-restricted flu-like manifestations to severe acute respiratory syndrome (SARS) with likely combination with multi-organ failure as a result of cytokine storm or hemophagocytic syndrome. In renal patients, the last conditions speak to a true test concerning care and endurance [6]. CKD patients are more susceptible to COVID-19 than the general population. Moreover, given that patients on haemodialysis are consistently managed in the same centres, these dialysis centres can become probable contamination vectors. During past pandemics, patients on dialysis had the higher mortality rate when compared to the general population [7].

Numerous case-reports and observational studies have stated the possibility of using drugs such as hydroxychloroquine, lopinavir/ritonavir, and IL-6 blocker to treat COVID-19, however, to date, no definitive FDA-approved antivirals are available to combat novel coronavirus. In this landscape, different methods of management have been developed for acute respiratory distress syndrome (ARDS) secondary to COVID-19 [8]. Furthermore, because of the unforeseen and rapid blast of the spread and the absence of new compelling treatments, healthcare professionals are measuring the impact of medications utilized for other viral infections [9] Presently, nephrologists are utilizing the recommnded medications with specific regard for the renal impairment degree, interactions with different drugs and, dialytic clearance in patients on dialysis [6]. In this review, we discuss the epidemiology, the pathophysiology, the clinical implications, and specific COVID-19 therapy in CKD patients.

1.1 Epidemiology

An epidemiological study reported a high rate of a severe infection due to COVID-19 with almost 25%, where the kidney is one of the primary organs influenced by the severe infection [10]. Both the presence of CKD at clinic confirmation and the advancement of acute kidney injury (AKI) during the COVID-19 have increased the risk of mortality [11]. In an observational study that assessed the contributing elements that has caused AKI in 161 emergency unit patients, the incidence rate of AKI was 28%. About 35% of the patients who manifested AKI had prior CKD (stages 3-5), in addition, 28% of the patients with CKD (stages 3-5) had no AKI [12].

Severe COVID-19 prompts AKI in 20% to 40% of severe cases, and it is associated with a higher risk of mortality [13,14,15]. A meta-analysis investigated the possible association between renal dysfunction including AKI and clinical manifestations (including severity and mortality) of COVID-19 cases; the authors reported that the high proportion of AKI in non-survival patients was 31% [16]. Patients who manifested COVID-19-associated AKI are at advanced risk of developing progressive CKD following the primary infection [17]. A prospective cohort study comparing COVID-19 with and without kidney abnormalities reported that patients with kidney irregularities were mostly men, at older age and had worse coagulation profile [18].

The incidence of COVID-19 in CKD patients differed from 0.7 to 47.6% [19, 20]. A possible

cause for the high risk of severe infection in CKD patients is their rate of all-type infections and the prevalence of cardiovascular diseases that are higher when compared to the general population [21]. A meta-analysis confirmed that CKD was unequivocally associated with more than two-folds higher disease severity with an OR= 2.22(95% CI: 1.14, 4.31) [22]. In addition, past literature estimated that CKD patients are at 14 to 16 times higher risk of pneumonia-related fatality in contrast to the general population [23]. There is a lack of data on the influence of COVID-19 disease on the kidneys' function in patients with mild-to-moderate infection. Nonetheless, kidney dysfunctions are seen in up to 20%- 63% of the critically ill hospitalized cases [13]. The mortality rate caused by COVID-19 in dialysis cases is altogether higher than that in the rest of the population (14.2-30.5% versus 2.9%) [8].

1.2 Pathophysiology

Similar to SARS, COVID-19 utilizes Angiotensin-converting enzyme 2 (ACE-2) to penetrate target cells [11]. After accessing the lungs, SARS-CoV-2 contaminates cells presenting specific cell surface receptors, for instance, ACE2; for example, alveolar type 2 cellsor CD147, which is expressed in not only lung cells but also in the kidney cells [24,25]. Moreover, immune complexes deposition of viral antigen or virus-induced antibody can also result in kidney damage. Another proposed approach is that in severe COVID-19 subjects, an elevated level of pro-inflammatory indicators, including IL2, IL10, IL7, GSCF, MCP1, and TNF-α was revealed, indicating the possible development of the cytokine storm that could damage the kidney, heart, lung, among other cells (Fig. 1) [26,27].

It must be noted that renal tubules are possibly the first to be infected with COVID-19 in CKD subjects. CKD subjects are typically older population with several existing morbidities. They present imbalanced ratios of CD4+/CD8+ T cells and reduced activity of natural killer NK cells. Furthermore, some CKD cases (mainly those with a glomerular disease) may require glucocorticoids and immuno-suppressants administration that in turn can cause the dysfunction of their immune system, making them more vulnerable to COVID-19. Numerous small arteries and capillaries in the kidney might be affected by COVID-19, and given that the blood passes through the kidneys multiple times daily, COVID-19 and the inflammatory cytokines in the blood flow can cause kidney impairment. Lastly, dialysis patients are perceived as a severe and more susceptible subgroup of CKD patients. Besides, they are continuously exposed to a probably infected area because their routine treatment generally requires three dialysis sessions per week. Consequently, being infected with COVID-19 might aggravate kidneys' dysfunction and even lead to death [7,28].

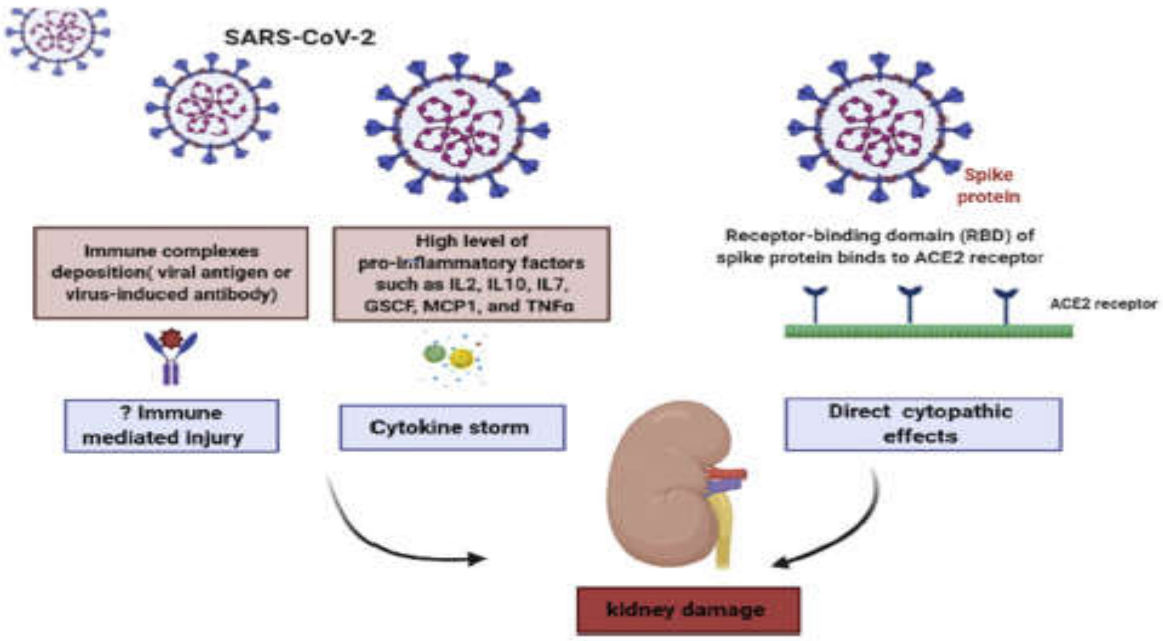

Fig. 1. Pathogenesis of kidney injury by SARS-CoV-2 [29]

1.3 Clinical Presentation

As an indicator of the disease, urine aalysis and proteinuria have confronted the examination of time [30]. Abnormalities in the kidney's function are presented as proteinuria (protein in the urine) and haematuria (red blood cells RBCs in the urine); some cases had high concentrations of plasma creatinine (19%) and urea nitrogen (27%) [13]. Many patients manifested proteinuria which could be associated with the cytotropic impacts of the corona virus on the podocytes. The expression of ACE2 can cause podocytes injury that, in turn, results in proteinuria [26].

Investigations showed that 15% of the COVID-19 cases that require hospitalization had one or more kidney dysfunction manifested by higher blood urea nitrogen levels or lower estimated glomerular filtration rate (eGFR), which is the best indicator of kidney function. Also, results from various cohort studies conducted on hospitalized patients indicated that 26% to 63% of cases had proteinuria at the day of admission or developed proteinuria during their hospital stay [18,31].

Specifically, proteinuria was correlated with a higher risk of (4-11 times) in-hospital mortality in COVID-19 cases contrasted to infected patients with normal kidney function, additionally, hematuria presented a higher risk of mortality by 12-folds. These hazard ratios (HR) were higher than other known risk factors, for example, older population (HR: 2.43), severe illness (HR: 6.10) and persisted significantly correlated with mortality even after adjusting for age, sex, severity, lymphocyte, comorbidity, hence showing that indicators of kidney damage have a significant task in evaluating the prognosis of subjects with COVID-19 [18,32,33].

A clinical study conducted on 59 COVID-19 patients stated that, regarding other renal markers, 19% of COVID-19 patients had raised concentrations of plasma creatinine, and 27% had high levels of urea nitrogen; CT scans showed that all of the investigated COVID-19 patients had renal damage [29]. Another investigation described that subjects with COVID-19presenting elevated baseline serum creatinine concentrations are at higher risk to be directed to emergency units and to go through mechanical ventilation, given that the existence of renal damage on hospital admission is related to more negative outcomes [11].

In addition, patients admitted with high serum creatinine levels were more likely to be men, at an older age (with median=73 years), and with a more critical presentation when compared to patients with typical serum creatinine levels (with median=61 years). Besides, patients with elevated baseline serum creatinine levels presented higher absolute count of leukocyte and lower lymphocyte and platelet counts. Patients with higher baseline serum levels of creatinine are more likely to manifest coagulation pathway disorders, including prolonged activated partial thromboplastin time and increased D-dimer levels. The number of patients with elevated procalcitonin, and plasma levels of aspartate aminotransferase and LDH are likewise higher in patients with CKD contrasted to those with ordinary renal function. The incidence of in-hospital mortality in patients with CKD was noted to be significantly higher when compared to patients with normal baseline serum creatinine levels [11].

1.4 Treatment

Currently, clinicians are applying the recommended COVID-19 therapeutics (Table 1) with specific consideration regarding the renal impairment level.

Disease-modifying and other significant prescriptions (such as erythropoietin invigorating agents ESA, intravenous iron, sodium-glucose-cotransporter-2 SGLT2 inhibitors, Renin-Angiotensin System (RAS) inhibitors, diuretics), generally administrated as an aspect of standard clinical care, require proper assessment, management, and consideration of patients' preferences [34]. Patients with advanced-stage CKD must recognize the advantages of disease-modifying drugs or other significant medications because of the COVID-19 pandemic. Special consideration must be given to ESA commencement among other treatments, due to its administration pathway and the particularities of how it is eliminated [34].

RAS and SARS-CoV-2 interactions, through the virus and ACE-2 liaison, have produced speculations of both likely damage and advantage of RAS inhibitor (RASi) use during the pandemic (Fig. 2) [35]. Proof supporting or invalidating these hypotheses are restricted at the hour of composing. Few investigations recommended ceasing from routine suspend of RASi throughout the novel outbreak. A national Canadian survey of advanced CKD clinics

approved these guidelines and further recommended temporarily suspending these medications in patients with manifestations of COVID-19, given the expanded risk of AKI and risk of mortality [34]. On the other hand, investigations that supported the absence of damage from proceeding with these medications in hospitalized COVID- 19 patients did not enrol patients with CKD (they were hypertensive patientsdiagnosed with COVID-19 or patients testing positive for COVID-19) [36, 37].

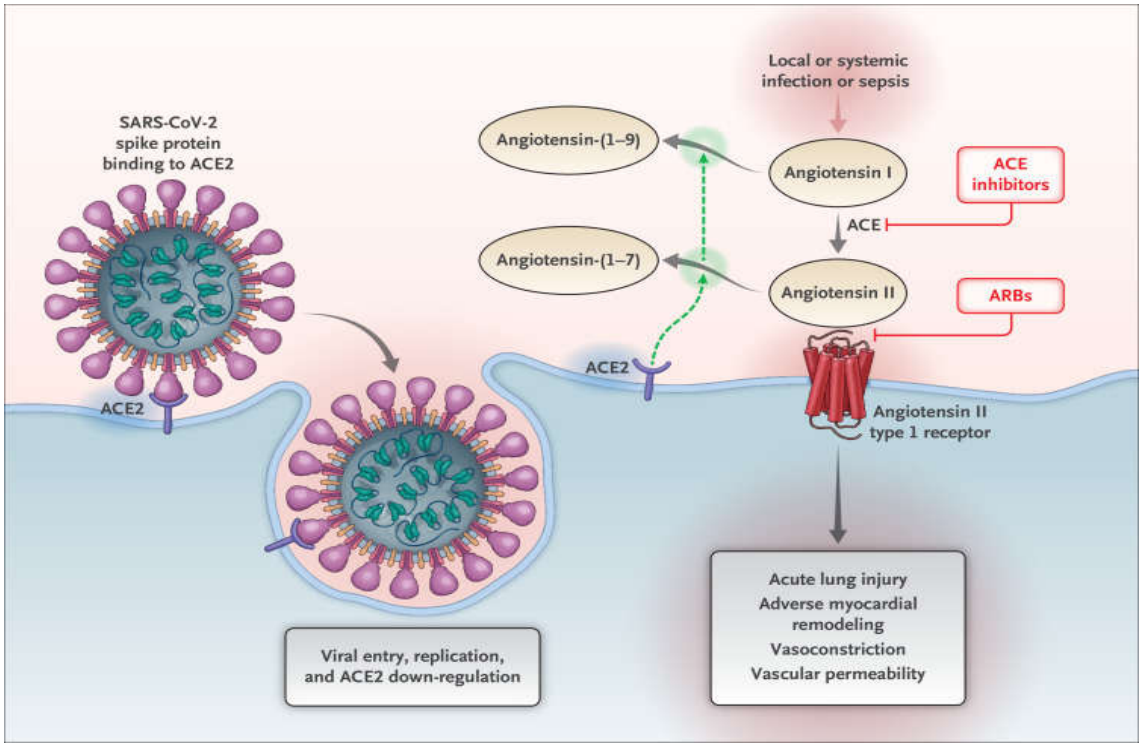

Fig. 2. Interaction between SARS-CoV-2 and the renin–angiotensin–aldosterone system [35]

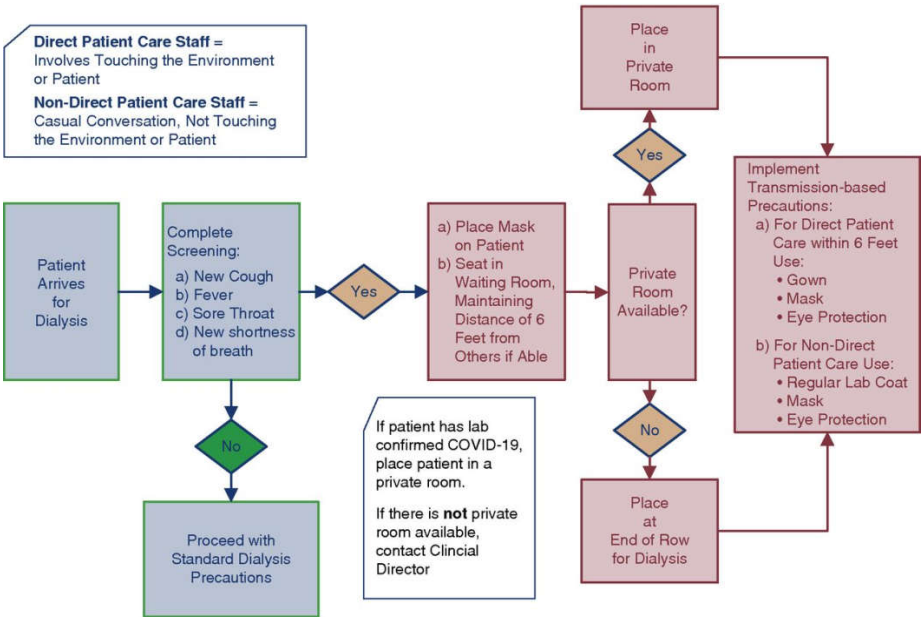

Fig. 3. Dialysis Patients screening for COVID-19 [42]

Table 1. Standard dose and renal dose at various kidney disease stages [6]

	Dose	Cr Cl> 50–90	Cr Cl 10–50	Cr CL< 10	Hemodialysis
			Antimalarials		
Cloroquine Phosphate	500 mg po q12h	500 mg po q12h	500 mg po q12h	Reducing half of the dose	Reducing half of the dose
Hydroxychloroquine Sulfate	200 mg po q8h or q12h	200 mg q8 h or q12h	Cr Cl 15–30: 200 mg q24h	Cr Cl< 15: 200 mg alterative days	200 mg alterative days
			Antibiotics		
Azithromycin	250–500 mg IV/ po q24h	250–500 mg q24h	250–500 mg q24h	250–500 mg q24h	250–500 mg q24h
Antivirals					
Lopinavir/ritonavir	400/100 mg po q12h	400/100 mg q12h	400/100 mg q12h	400/100 mg q12h	400/100 mg q12h
Favipavir	1600 mg po q12h on Day 1 then by 600 mg q12h	No data	No data	No data	No data
Remdesivir	200 mg po q24h on Day 1 then 100 mg q24h	200 mg po q24h on Day 1 them 100 mg q24h	Cr Cl 50–30: 200 mg po q24h on Day 1 then 100 mg q24h	Cr Cl< 30: Avoid use	Avoid use
			Monoclonal antibody		
Tocilizumab	8 mg/Kg q12 h	without any adjustment	without any adjustment	without any adjustment	without any adjustment
Eculizumab	900 mg IV every 7 days	without any adjustment	without any adjustment	without any adjustment	without any adjustment
			Corticosteroids		
Dexamethasone	1–2 mg/Kg IV/ po q24h	1–2 mg/Kg q24h	1–2 mg/Kg q24h	1–2 mg/Kg q24h	20 mg q24h for 5 days then 10 mg q24h for 5 days
Methylprednisolone	40–80 mg IV q24h	40–80 mg IV q24h	40–80 mg IV q24h	40–80 mg IV q24h	No data

Cr Cl: creatinine clearance; IV: intravenous; Po: oral dosage

The impacts of discontinuation of RASi or switching medications are questionable among CKD patients. In China, despite the low CKD among hospitalized patients with COVID-19 (1-3%), the frequency might be elevated among severe patients and those in other geographic districts [35,38]. For these high-risk cases, it is recommended to present individualized treatment choices concerning the continuation of RAAS inhibitors in the light of hemodynamic status, renal capacity, and clinical stability [35]. COVID-19 poses a particular menace to CKD patients, particularly to those on dialysis and kidney transplant recipients. Those getting dialysis must keep on getting their dialysis treatments and respect their physician's guidelines [39]. Patients with a kidney transplant are ought to embrace the measures prescribed to prevent disease occurrence. The Taiwanese and Chinese Societies of Nephrology have created recommendations for dialysis units during the COVID-19 pandemic. Nevertheless, the American Society of Nephrology/Center for Disease Control (CDC), and the European Renal Association (ERA-EDTA) presented some basic protective measures to minimize COVID-19 dissemination in dialysis offices such as expanding prevention efforts, establishing universal screening, and isolating subjects with COVID-19, and addressing them to assigned haemodialysis centres [40,41]. A recent study provided preventive policies and procedures including a) symptoms and temperature screening for both dialysis patients and staff, b) disinfection for specific areas, and c) using Personal Protective Equipment PPE [42]. The establishment of the Kidney Disease/ Improving Global Outcomes (KDIGO) supportive care guideline (such as restraint of nephrotoxins, routine monitoring of serum creatinine and urine output, consideration of hemodynamic monitoring) in severe subjects with kidney dysfunction could possibly decrease the development and severity of AKI in COVID-19 yet still requires validation [43].

Furthermore, a recent study reported principal treatments currently used against COVID-19 [6]. These drugs must be used with causation in patients with different degree of CKDs including those on dialysis Table 1.

1.5 Severity and Outcomes

CKD is an important risk factors for severe COVID-19 [44]. The mortality is higher among hospitalized COVID-19 patients with CKD in comparison to those without CKD [45]. The mortality is higher in haemodialysis and CKD patients compared to renal transplant patients. Renal transplant patients.

2. CONCLUSION

COVID-19 may worsen the impaired kidney function and may increase mortality. Care givers should pay especial attention to medications dosing in COVID-19 patient with CKD history.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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