RENAL MANIFESTATIONS AND COMPLICATIONS OF COVID-19

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ABSTRACT

In December 2019, the Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was brought to the fore as the cause of the rapidly spreading Coronavirus disease-19 (COVID-19) that soon became a global pandemic with rising death tolls.

The disease was initially described as a primary respiratory infection, however as studies advance, its effects on the kidneys have also been descibed. The role of the Angiotensin-converting enzyme 2 receptor found in abundance in both the lungs and the kidneys has been implicated in the pathophysiology of kidney disease following kidney infection.

This article discusses the aetiology, pathogenesis, and management of acute kidney injury (AKI) and chronic kidney disease (CKD) in COVID-19 and the peculiarities of the infection in patients with end-stage renal disease on renal replacement therapy (dialysis and kidney transplant).

INTRODUCTION

The Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) derives its name from its structure – a spherical virion with nine spike proteins. It belongs to the beta coronavirus subfamily alongside the SARS-CoV[1]. The first incidence of the COVID-19 disease, caused by the SARS-CoV-2, was reported in Wuhan in December 2019[2,3]. The disease was eventually declared a pandemic on March 11, 2020[4], and has gone on to cause many deaths and morbidities worldwide. COVID-19 has also caused extensive social, mental, and socio-economic impacts. As at June 2022, about 6.25 million people have died from the disease out of the 514 million cases that have occurred worldwide.

Following the study of trends in cases, advanced age has been identified as the main risk factor for mortality in COVID-19 cases. Apart from advanced age, outcome is also poor with co-existent conditions such as chronic kidney disease, diabetes, hypertension, chronic obstructive pulmonary disease, obesity, and tumours [5,6,7]. As medical scientists continue to understand the disease, the impact of COVID-19 disease outside the primarily affected organ – the lungs – is continually unravelled[8]. New evidence currently indicates that the effect of COVID-19 disease on the kidneys is more common than previously understood and may affect individuals on chronic dialysis and kidney transplant recipients more uniquely than others without these morbidities[9].

AETIOPATHOGENESIS OF KIDNEY INJURY

The incidence of Acute Kidney Injury (AKI) in COVID-19 ranged from 0.5 to 56.9% based on different definitions of AKI used and the populations studied. A higher risk of AKI was also associated with the black race. Some studies also found that AKI as a complication of COVID-19 infection (AKI stage three or AKI requiring renal replacement therapy) increased the mortality rate by about three folds[10,11,12].

Many explanations have been put forward regarding the link between COVID-19 and the kidneys and the damage mechanism. One of the explanations is the role of the Angiotensin-Converting Enzyme 2 in the pathophysiology of kidney damage secondary to COVID-19 infections, which is similar to the mechanism of kidney damage exerted by SARS-CoV discovered in 2003. Angiotensin II is formed from the conversion of angiotensinogen to angiotensin I which is formed from the cleavage of angiotensinogen by renin[13]. This could be described as a more direct mechanism leading to tubular damage. Angiotensin II is a systemic vasoconstrictor that also causes inflammation, endothelial cell dysfunction, fibrosis, etc. ACE2 is an enzyme that breaks down angiotensin II to form angiotensin I-7, which reduces the inflammation caused by angiotensin II.

There is an abundance of ACE 2 expression in organs like the bronchus, lung parenchyma, heart, gastrointestinal tract, and kidneys[14]. SARS-CoV uses ACE2 as a receptor for cell entry and leads to the downregulation of the expression of the enzyme once it is in the cell[14]. This downregulation

then leads to the elaboration and unbridled action of angiotensin II. Evidence of the cell entry receptor pathway in the kidneys was demonstrated by the presence of ACE2 expression in the kidneys 100-fold more than in the lungs, following human tissue RNA-sequencing data[10,14]. This implies that in the kidneys where the expression of ACE2 is abundant, there is a higher degree of damage from the SARS-CoV 2.

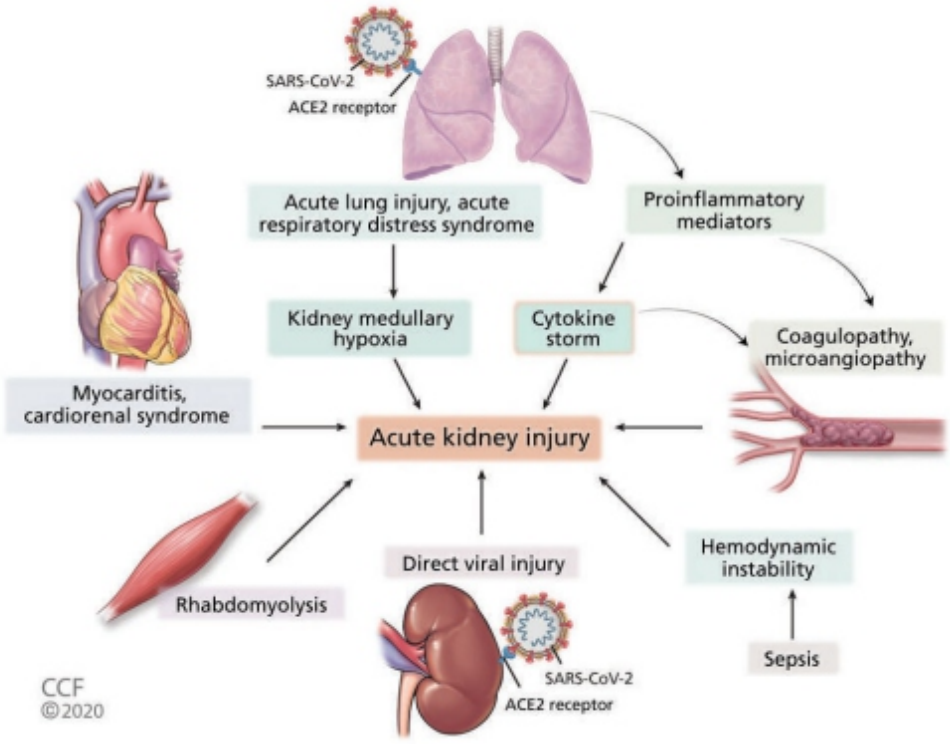

Figure 1. Pathophysiology of acute kidney injury in COVID-19 (ACE2 = angiotensin-converting enzyme 2; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2). Adapted from Hassanein et al, 2020.

Some indirect mechanisms of kidney damage in COVID-19 infection have also been explained following extensive research. Acute lung injury can cause AKI through hemodynamic changes and by the reduction of cardiac output with high intrathoracic pressure, elaboration of cytokines that lead to systemic inflammation and reduction in blood flow to the medulla of the kidney due to hypoxemia [15,16,17].

Sepsis is associated with increased risk of AKI in infections, generally. This kidney damage results from higher levels of inflammatory cytokines and maladaptive immune responses that occur alongside hypoperfusion of the kidney[18]. Cardiorenal syndrome could also lead to AKI in COVID-19 patients; Damage to the cardiovascular system in the form of cardiomyopathies and viral myocarditis could lead to hemodynamic instabilities and eventual decreased perfusion of the kidneys[17].

Acute kidney injury can also result from the direct cythopathic effect of the SARS CoV 2 virus on the renal tubular and glomerular cells. Patients, especially the elderly, suffering from COVID-19 infection may experience dehydration due to fever or a reduction in fluid intake which may result in reduction in blood flow to the kidney and eventual acute tubular necrosis [19,20].

Studies of the SARS CoV virus revealed that rhabdomyolysis may result from direct attack of the virus on muscle cells, eventually leading to AKI. This mechanism has also been considered in the pathophysiology of acute kidney injury in COVID-19 infections[19,20]. Patients with COVID-19 infection may experience multiple organ failure and may need to be on prolonged ventilator support which could predispose to acute kidney injury.

Kidney tubular damage can be caused by viral infection through the deposition of Membrane Attack Complex on tubules and the entry of CD68+ macrophages into the tubular cells[21]. Autopsies of patients with COVID-19 revealed damage to proximal tubules, degeneration of vacuoles, aggregation of erythrocytes in the peritubular and glomerular capillaries without fragmentation and obstruction without fibrin thrombi were observed. This was however said not to be confirmatory of direct kidney damage[22].

Cytokine storm syndrome, with the elaboration of IL-6 and IL-8 induced by viral infections like the COVID-19

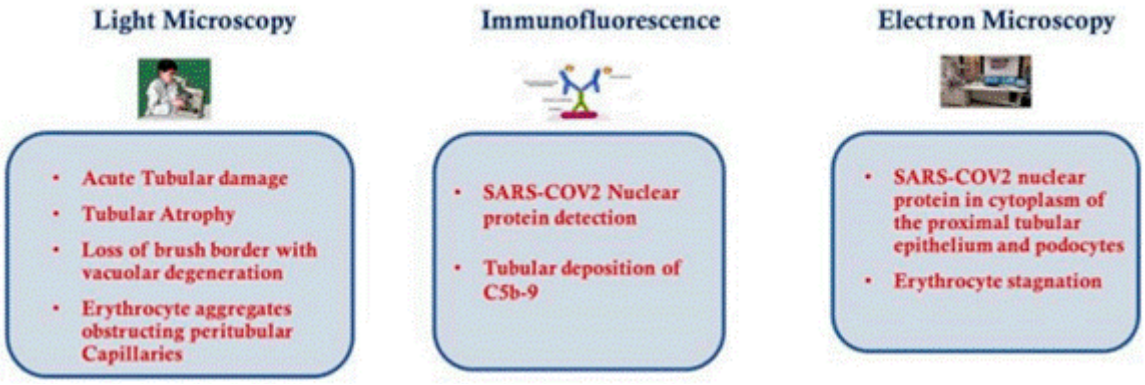

Figure 2: Image showing the histological features of kidney from COVID-19 patients. Adapted from Gagliardi et al, 2020.

infection may lead to the adhesion of inflammatory cells to the endothelium of blood vessels, vasodilatation and eventual renal injury. However, recent research showed an absence of SARS-CoV-2 RNA in kidney tissue, making it unlikely that cytokine storm leads to podocyte injury via elaboration of APOLI expression[23,24].

Causes of acute kidney injury in COVID-19 patients

Cause	Supporting evidence
Prerenal (volume depletion)	Increased blood urea nitrogen: creatinine ratio (> 20), urine sodium < 20 mmol/L, fractional excretion of sodium < 1%
	Urine sediment may show hyaline casts
Acute tubular injury	Urine sodium > 20 mmol/L, fractional excretion of sodium > 1%
	Urine sediment with granular or muddy brown casts
Acute interstitial nephritis	Rash, eosinophilia, white blood cells on urine microscopy
	Urine sediment with white blood cell casts (urine eosinophils are not sensitive or specific)
Postrenal (obstruction)	Bladder scan with high postvoid residual volume, oliguria improving with Foley catheter placement
	Kidney ultrasonography showing hydronephrosis
Rhabdomyolysis	Increased serum creatine kinase and myoglobin in urine
	Positive urine dipstick for blood, no red blood cells on microscopy
Abdominal compartment syndrome	Increased intra-abdominal pressure (> 20 mm Hg)
Coagulopathy	Elevated prothrombin time, partial thromboplastin time, D-dimer, fibrinogen
Cardiorenal syndrome	Jugular venous distention, low ejection fraction on echocardiography, urine sodium < 20 mmol/L

Figure 2: A table showing a summary of the causes of acute kidney injury in COVID-19 patients. Adapted from Hassanein et al, 2020.

The association between COVID-19 infection and chronic kidney disease is mostly a predisposition to the former by the latter. Patients with CKD have a higher risk of developing upper respiratory tract infection, pneumonia and COVID-19 infection due to their constant proinflammatory state and immunosuppression (10,25). A meta-analysis involving 53,000 patients with COVID-19 revealed that CKD was associated with a 6 fold risk of severe infection compared with patients without CKD.

MANAGEMENT OF ACUTE KIDNEY INJURY

The management of acute kidney injury associated with COVID-19 is currently mostly supportive, with the avoidance of nephrotoxic drugs and the early start of renal replacement therapy. Continuous renal replacement therapy was effective in treating acute kidney injury associated with SARS, MERS, and sepsis and is effective in COVID-19 infections and the multiple organ failure that might be associated with it[10,26].

COVID-19 AND CHRONIC KIDNEY DISEASE (CKD)

It is well known that patients with CKD have a higher risk of upper respiratory tract infection and pneumonia as a result of their functional defects in innate and adaptive immunity as well as a persistent proinflammatory state[10]. There is an increased risk of severe COVID-19 infection in patients with pre-existing renal disease, especially chronic kidney disease[25]. It is therefore imperative that adequate COVID-19 precautions and be taken to limit exposure of these patients. In addition, close monitoring is required for hospitalised patients with CKD. In one meta-analysis involving 53,000 patients with confirmed COVID-19 disease, patients with CKD were found to have a 6 fold higher risk of severity of the infection when compared with those without CKD [27]. A similar study[25] showed that up to 20% of patients with CKD who contracted COVID-19 had a 3 times the risk of severe disease compared to COVID-19 infected patients without CKD. Routine follow-up is equally required for patients in convalescence from AKI secondary to COVID-19 as well as patients with proteinuria and / or haematuria in the absence of AKI as one comparison study demonstrated a higher prevalence of chronic kidney disease in patients with COVID-19 and AKI those without AKI[37]

COVID-19 IN RENAL TRANSPLANT PATIENTS

Renal transplantation generally poses an increased risk of infection due to immunosuppression from depressed T-cell responses. Indeed kidney transplant recipients are more susceptible to SARS-CoV-2 infection and rapid progression of the COVID-19 compared to the general population[44]. In addition to the immunosuppressive therapy mediated depressed T-cell responses in them, infection with SARS-CoV-2 virus has also been shown to reduce the population and functional capacity of T-cells which are critical in antiviral immune response[48]. The risk of infection is highest in the first 3 months following the procedure with patients who receive induction therapy with lymphocyte-depleting agents being notably affected[40]. Prevention of SARS-CoV2 infection in these patients starts with effective screening of donors. In renal transplant recipients who contract the infection, the most frequently reported symptoms by far are fever, cough, and myalgias[41], all of which may not be present in any one patient[42]. Of note, some renal transplant patients with COVID-19 may present with low-grade fever, mild cough, and normal leukocyte count. These milder symptoms are probably the result of a protective effect of concurrent immunosuppressive therapy against the cytokine storm in these patients [43]. Hence, it may be necessary to lower the threshold for COVID-19 testing in renal transplant recipients.

In the therapeutic management of renal transplant patients with COVID-19 it is not necessary to change the usual immunosuppressive therapy regimen, however, most authors recommend a tapering down of immunosuppressives because of the possibility of over-whelming infection. This should be done alongside initiation of antiviral, antibiotic, and anti-inflammatory therapy [39,40.41.42,43,44]. The protease inhibitors ritonavir and lopinavir, as well as the broad spectrum antiviral, remdesivir have shown promising results[9, 45]. However, concurrent use with protease inhibitors can cause elevated calcineurin inhibitor levels necessitating a substantial reduction in the dose of calcineurin inhibitors[9, 42]. Discontinuation of mycophenolate mofetil (and other antiproliferatives) while lowering the dose of calcineurin inhibitors and glucocorticoids has been deemed beneficial in these patients [9,39,40.41.42,43,44]. In renal transplant patients with COVID-19 who have unconfirmed pneumonia, complete withdrawal of immunosuppressants especially calcineurin inhibitors is discouraged[39]. However, in critically ill patients, it has been suggested that withdrawal of immunosuppression can safely be done while converting these patients to hydrocortisone/solumedrol. Although this approach may hasten viral clearance, it presents an increased risk of immune reconstitution with consequent graft rejection [14, 49, 50]. A safer alternative is the reduction of tacrolimus rather than complete withdrawal[14]. More so, some authors have reported antiviral and anti-inflammatory properties of calcineurin inhibitors [51, 52]. A possible role of the IL-6 receptor antagonist Tocilizumab in reducing inflammation has also been suggested[46,47].

Nevertheless, all of these strategies do not preclude the need for strict isolation measures and infection prevention protocols among staff caring for these patients. Upon recovery, gradual reintroduction of immunosuppressive therapy is recommended[39,40.41.42,43,44].

COVID-19 IN CHRONIC DIALYSIS PATIENTS

While it is clear that AKI is a major indicator of poor prognosis in COVID-19 disease and CKD increases the risk of severe infection, the impact of the infection on end-stage renal disease remains largely unclear[9].

In an earlier study by Wang et al.,[28], the incidence of COVID-19 among 230 patients on HD was found to be 16.09%. Affected patients presented mostly mild symptoms and 7 of HD patients ended up dying with COVID-19. However none of the deaths were the direct result of COVID pneumonia. The causes of death were heart failure,

hyperkalemia, and cerebrovascular disease [29]. In a larger retrospective multicenter study of 7,154 patients on hemodialysis, the prevalence of COVID-19 was found to be 2% with 50% of patients presenting with fever and 20% of patients without any symptoms[30]. The mortality rate among patients on dialysis with COVID-19 is greater than the general population[30,31].

Frequent circuit clotting poses a major challenge during continuous dialysis in COVID-19 patients[13]. This challenge is thought to be a consequence of coagulation system upregulation by elevated inflammatory cytokines in COVID-19[38]. Hassanein and colleagues[13] noted that circuit clotting seems to improve when heparin was administered through the circuit prefilter. Another challenge encountered in managing patients on dialysis with COVID-19 is positioning. In order to maintain adequate ventilator support in the prone position for patients with acute respiratory distress syndrome and haemodialysis in the supine position, it is important to have a definitive time-bound protocol in place[13]. Care must be taken the safety of vascular access during change of positioning.

Among patients infected with COVID-19, levels of proinflammatory cytokines and circulating natural killer cells as well as cytotoxic and helper T cells are significantly lower in patients on hemodialysis compared to those who were not [29]. Interestingly, patients with COVID-19 on haemodialysis were much more likely to present mild symptoms compared to patients not receiveing haemodialysis. In addition, the risk of developing acute respiratory distress syndrome was lower in them compared to COVID-19 patients not on hemodialysis [29]. Although at a glance, it may appear that hemodialysis offers some benefit for patients with ESRD infected with SARS-CoV2, the same cannot be said for patients with ESRD on hemodialysis who are uninfected. The reduced inflammatory response in uninfected patients undergoing hemodialysis actually predisposes them to SARS-CoV-2 infection[9, 32]. The time it takes to clear the virus is also prolonged in patients on hemodialysis as a result of impaired immune response in them[29,33].

This calls for additional preventive measures to limit infection spread in these patients. Current recommendations include prompt recognition and isolation of individuals with respiratory infection and isolation of these patients from other patients on hemodialysis.

Where facilities are available, symptomatic COVID-19 patients should be preferably dialyzed in a separate dialysis room otherwise the management of these patients should be at a location directly from the main traffic flow to limit exposure of other patients on dialysis[34]. The recommendation is for a distance of at least 2m from other patients in all directions and care should be provided by specifically designated health care workers[35].

The place of standard contact and droplet precautions, including personal protective equipment must not be neglected and should take utmost priority[34]. During routine clinical visits, face masks, and eye shields are sufficient, while during high-risk procedures, N95 respirators and other respiratory protection devices are required. It has been suggested that patients on peritoneal dialysis be managed from home and whenever possible, consultation or assistance be provided with telemedicine unless otherwise indicated[36]. The goal must be to prevent infected among patients on dialysis and ensure uninterrupted dialysis for infected patients while following the best available evidence in managing COVID-19 in these patients.

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