COVID-19 and Kidney Injury

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ABSTRACT

BACKGROUND: Acute kidney injury (AKI) has been reported as a complication of COVID-19. However, the epidemiology, management, and associated outcomes have varied greatly between studies. The pathophysiology remains unclear.

SUMMARY: The etiology of AKI in the setting of COVID-19 appears multifactorial. Systemic effects of sepsis, inflammation, and vascular injury likely play some role. Furthermore, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 receptor, highly expressed in the kidney, providing a route for direct infection. Older age, baseline comorbidities, and respiratory failure are strong risk factors for the development of AKI. Regardless of etiology, AKI carries a significantly increased risk for in-hospital mortality, especially in those with critical illness. Currently, management of AKI in patients with COVID-19 remains supportive.

KEY MESSAGES: AKI is common in patients with COVID-19. Future studies are needed to examine the response to anti-viral treatment as well as long-term renal outcomes in patients with AKI.

KEYWORDS: acute kidney injury, COVID-19, ACE2

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) outbreak, first reported on December 8, 2019 in Wuhan, China, was designated as a pandemic by the World Health Organization (WHO) on March 11, 2020. This disease, recognized as an infection by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread quickly throughout the world. As of August 4, 2020, close to 18 million laboratory-confirmed cases had been documented globally, with nearly 700,000 deaths worldwide.[1] The mortality rates vary significantly among studies from 0.3% to 10%, partially reflecting the differences in local policy, access to diagnostic testing, and health care resources and response. Clinical presentations of COVID-19 can range from asymptomatic infection, self-limited influenza-like symptoms, acute pneumonia to severe respiratory failure.

The ongoing COVID-19 pandemic carries serious medical, psychosocial, and economic consequences. Understanding its pathophysiology, clinical course, management strategy and therapeutic response are of paramount importance. Here, we will synthesize the current literature on the acute kidney injury (AKI) in COVID-19, and discuss its epidemiology, pathogenesis, clinical features, outcomes, and management strategies.

ACUTE KIDNEY INJURY

COVID-19 has life-threatening effects far beyond its respiratory manifestations. An initial single center cohort of 116 confirmed COVID-19 cases from China with a median age 54, 11 of whom had severe infection, failed to show incident AKI. [2] However, subsequent studies have reported a cumulative incidence of AKI in COVID-19 ranging from 0.9% to 29%, with patients who were critically ill more likely to develop AKI. A summary of some of these studies can be seen in **Table 1**.

The earliest publication identifying AKI as a consequence of COVID-19 came from China, involving a large cohort of 1099 hospitalized patients with confirmed COVID-19 and a median age of 47. Five percent of this cohort was critically ill requiring ICU admission. Interestingly, these patients were relatively healthy at baseline: 7% had history of diabetes mellitus (DM), 15% hypertension, and only 1% chronic kidney disease (CKD). AKI was rare with an incidence rate of 0.5%.[3] In a second Chinese cohort from Wuhan, Cheng et al examined 701 hospitalized patients with COVID-19, of which 10% required intensive care.[4] These patients were older and with more baseline comorbidity; AKI was found in 5.1% of patients. Baseline CKD was a strong risk factor for the development of AKI. Consistent with this, Wang et al reported a 4% AKI incidence rate in another, smaller Chinese cohort with similar age and baseline comorbidity.[5]

In the United States, two large cohorts from metropolitan New York have helped define the epidemiology of AKI here. A cohort of 5,449 patients from 13 academic and community hospitals, with heavier burden of comorbidities than in the Chinese cohorts, had an incident AKI rate of 36.6%.[6] AKI developed early in the course, with more than one third of those with AKI either arriving with it or developing it within 24 hours of admission. AKI was primarily

Table 1. Summary of published studies on AKI in patients with COVID-19

Studies	Origin	N	Age	DM	HTN	CKD	ICU	AKI	Mortality (overall)
Cheng et al[4]	China	701	63 (50–71)	100 (14%)	233 (33%)	14 (2%)	73 (10%)	36 (5%)	113 (16%)
Wang et al[5]	China	138	56 (42–68)	14 (10%)	43 (31%)	4 (3%)	36 (26%)	5 (4%)	6 (4%)
Guan et al[3]	China	1099	47 (35–58)	81 (7%)	165 (15%)	8 (1%)	55 (5%)	6 (0.5%)	15 (1%)
Hirsch et al[6]	USA	5449	64 (52–75)	1797 (33%)	3037 (56%)	N/A	1395 (26%)	1993 (37%)	888 (16%)
Yang et al[22]	China	52	60 (13)	9 (17%)	N/A	N/A	52 (100%)	15 (29%)	32 (62%)
Chan et al[7]	USA	3235	N/A	N/A	N/A	N/A	815	1406 (46%)	N/A

Data was reported as median (IQR), mean (SD) or number (%)

seen in COVID-19 patients with respiratory failure (23.2% in ventilated patients vs. 0.2% in non-ventilated patients). Of patients who required ventilation and developed AKI, 52.2% had the onset of AKI within 24 hours of intubation. Among patients with AKI, 14.3% received renal replacement therapy (RRT), and the vast majority (96.8%) were on ventilators. Risk factors for AKI included older age, DM, cardiovascular disease, black race, hypertension, and need for ventilation and vasopressor support. For patients who developed AKI and survived to hospital discharge, the median peak serum creatinine was 2.34 mg/dL with a median of 1.70 mg/dL at discharge. In another large cohort of 3,235 hospitalized COVID-19 patients from New York, AKI occurred in 46% patients with 20% requiring RRT.[7] The cumulative incidence of AKI (admission plus new cases) in patients admitted to the intensive care unit was 68%. In the entire cohort with AKI, the proportion with stages 1, 2, and 3 AKI were 35%, 20%, 45%, respectively. In those needing intensive care, the respective proportions were 20%, 17%, 63%, suggesting an association between severe AKI and severe illness. Of those with AKI in the ICU, 34% received renal replacement therapy. Independent predictors of severe AKI in this cohort included CKD, higher systolic blood pressure, and potassium at baseline.

In a meta-analysis of nine studies (eight from China, one from United States) of hospitalized patients with COVID-19, two of the studies included only patients admitted to the intensive care unit.[8] In an overall hospital setting, the incidence rates of AKI varied from 0% to 14.7%, with a pooled incidence rate of 7%. In the six studies that reported RRT use, 0.5%–7.3% of patients required RRT, with a pooled RRT incidence rate of 2%. Four studies reported the incidence of AKI in the ICU setting, with rates ranging from 8.3% to 28.8% and a pooled incidence rate of 19%. Only three studies reported RRT use in an ICU setting, with rates of RRT use ranging from 5.6% to 23.1% with a pooled rate of 13%. These studies reiterate that the risk of AKI and need for RRT were much higher in COVID-19 patients who were critically ill.

In addition to AKI from acute tubular necrosis, the possibility of glomerular disease from COVID-19 has been suggested with the presence of hematuria and proteinuria (**Table 2**). In the Chinese cohort by Cheng, et al, 44% of patients had proteinuria and 27% had hematuria at presentation.[4] In the US cohort by Hirsch et al, 42% had proteinuria and 46% had hematuria.[6]

Table 2. Summary of COVID-19 related kidney pathological findings in patients with acute kidney injury. Summarized from 9–11.

Tubulointersitial
Acute Tubular Injury
Vascular
Cortical infarction
Microthrombi
Glomerular
Anti-Glomerular Basement Membrane Nephritis
Collapsing Focal and Segmental Glomerulosclerosis
Membranous Nephropathy
Minimal Change Disease

PATHOLOGICAL FINDINGS

According to an autopsy series from Wuhan, China, light microscopy of the kidney tissue from those with AKI (nine patients total) showed findings consistent with acute tubular injury, the pathologic correlate of acute tubular necrosis (ATN): loss of brush border, vacuolar degeneration, luminal dilatation, and in some cases, areas of necrosis and detachment of tubular epithelium.[9] Pigmented tubular casts, possibly due to rhabdomyolysis, were also seen. Distal tubules and collecting ducts showed only occasional cellular swelling and edematous expansion of the interstitial space without significant inflammation. Acute pyelonephritis was observed in some patients. Diffuse erythrocyte aggregation and obstruction were present in peritubular and glomerular capillaries without distinct fragmentation of erythrocytes, or features of fibrin thrombi. In glomeruli, segmental fibrin thrombus in capillary loops were found with severe endothelial swelling and injury, along with other ischemic changes and pseudocrescent appearance. Immunofluorescence showed nonspecific IgM and C3 trapping. Under electron microscopy, paramesangial and subendothelial electron dense deposits with segmental mesangial interposition and increased lamina rara interna were present in one case, and

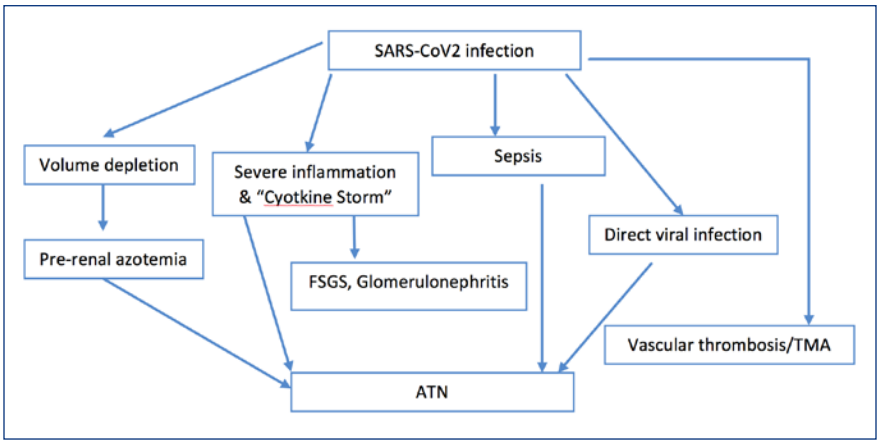
scattered subepithelial deposits were noted in another case. Both patients did not have evidence of bacterial infections, suggesting a direct association with SARS-CoV-2 infection. No other diagnostic electron-dense deposits were detected.

Two separate biopsy series taken from patients in the United States who developed AKI in the setting of COVID infection has found new-onset immune-mediated glomerular disease[10] and the presence of collapsing focal and segmental glomerulosclerosis in patients with two apolipoprotein L1 risk variant genes.[11] No intracellular viral particles were observed in these cases.

PATHOGENESIS

The causes of AKI are likely multifactorial (**Figure 1**). In addition to common processes related to systemic infection including poor renal perfusion from volume depletion or blood flow shunting, direct cytopathic viral infection, severe inflammation and cytokine storm resulting from SARS-CoV2 infection have all been implicated.[9,12,13] The contribution of each of these entities to tubular injury remains under investigation. As noted above, the vast majority of cases are caused by ATN, although some glomerular pathologies have been found. In the cases of glomerular involvement, the absence of viral particles in these series suggests cytokine-mediated kidney damage as the likely etiology, but further investigation to confirm this is required. Lastly, COVID-19 has been shown to cause endothelial injury and is associated with hypercoagulable state,[14] thus renal thrombotic microangiopathy (TMA) or microvascular thrombosis can also contribute to the development of AKI.

Figure 1. Pathogenesis of AKI in COVID-19



DIRECT VIRAL INFECTION OF KIDNEY

Similar to SARS-CoV, the spike (S) protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), its host cell target for direct invasion. The viral entry into the host cells also require viral S protein priming by cellular proteases, the TMPRSS family, which entails S protein cleavage and allows fusion of viral and cellular membranes.[15] ACE2 is highly expressed in the kidney, similar to the epithelial cells of lung and gastrointestinal (GI) tract, indicating kidney as a potential target organ.[16] Via single-cell transcriptome analysis, Pan et al demonstrated that both ACE2 and TMPRSS genes were significantly co-expressed in podocytes and renal proximal tubules, and the levels of expression were higher than that of lung tissue and GI tract.[16]

The more direct evidence of viral kidney infection came from an autopsy series in Wuhan, China. Su et al reported pathologic findings in the kidneys from 26 patients died of SARS-CoV-2 infection.[9] Nine of the 26 had clinical evidence of kidney involvement with increased serum creatinine and/or new-onset proteinuria. Electron microscopic examination revealed clusters of coronavirus particles with distinctive spikes in the tubular epithelial cells and podocytes. The immunostaining for SARS-CoV-2 nucleoprotein was positive in renal tubules, as well. There was also strong focal viral staining in parietal epithelial cells as well as occasional weaker staining in podocytes. As expected, the expression of ACE2, the receptor of SARS-CoV-2, was found to be upregulated in these patients infected with COVID-19. Compared with non-COVID-19 infected control, ACE2 expression was prominent in proximal tubular cells, particularly in areas with severe tubular injury. [9]

CYTOKINE STORM AND INFLAMMATION

Induction of an inflammatory response is a known trigger for AKI, and it is initiated through both pathogenic and non-pathogenic processes. During inflammation, pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) bind to Pattern Recognition Receptors (PRRs) expressed in cells of multiple organs, including renal tubular epithelial cells, and induce cell damage.[17] As a matter of fact, there is a strong association between cytokine levels (interleukin (IL)-6, IL-10, and macrophage migration inhibitory factor) and the development of sepsis-induced AKI.[18]

An inflammatory cytokine profile resembling hemophagocytic lymphohistiocytosis has been found in severe cases of COVID-19, characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α.[12] According to a retrospective study of 150 COVID-19 cases in Wuhan, China, elevated levels of inflammatory markers such as ferritin, C-reactive protein and IL-6 were present in severe COVID-19 cases and predicted fatality,[13] suggesting

an important and detrimental role of virally driven hyperinflammation and cytokine storm in SARS-CoV-2 infection. The higher risk and severity of AKI seen in severe SARS-CoV-2 infections supports the role of inflammation in the pathogenesis of AKI.

VASCULAR INSULT AND COAGULATION DISORDER

Cardiovascular complications are rapidly emerging as a key threat in COVID-19. Direct endothelial cell infection and endothelitis have been demonstrated in SARS-CoV2 infected patients.[19] Recruitment of immune cells, either by direct viral infection of the endothelium or immune-mediated, can result in widespread endothelial dysfunction. Injured endothelial cells produce a decreased quantity of vasodilators, such as nitric oxide, resulting in a more pronounced response to vasoconstrictors. This leads to a redistribution of blood flow.[17] The imbalance between vasoconstrictors, vasodilators and oxidative stress at the endothelial level is believed to be a major contributor to the development of AKI.

The development of coagulopathy in the forms of deep venous thrombosis and pulmonary embolism are well-recognized features of COVID-19, and is one of the most significant poor prognostic factors.[20] Therefore, augmented vasoconstriction, small vessel occlusion due to activated endothelial cells and activation of the coagulation system can result in renal TMA and compromised microvascular perfusion. Lastly, patients with severe COVID-19 who experienced abnormal clotting have been shown to carry positive antiphospholipid antibodies, suggesting secondary antiphospholipid syndrome might also account for COVID-19-associated thrombotic events.[14]

MANAGEMENT OF AKI IN THE SETTING OF COVID-19

To date, there are limited data to guide the clinical treatment strategies for COVID-19 and its renal complications. For COVID-19, the general approaches include controlling the source of infection, use of personal protective equipment to reduce the risk of transmission, early diagnosis/isolation, and symptomatic supportive care for affected patients. Antibacterial agents are ineffective, and no antiviral agents have been clearly proven to be beneficial for treating COVID-19.

In those with AKI, early detection and adoption of kidney protective measures are important to reduce mortality and improve prognosis. Strategies have been applied including hemodynamic support, avoidance of nephrotoxic drugs, aggressive management of electrolyte and acid-base derangements, and renal replacement therapy whenever it is indicated.

For patients who require dialysis, clinicians can decide to provide either intermittent hemodialysis, continuous renal replacement therapy (CRRT) or acute peritoneal dialysis based on a patient's clinical status and the facility's resources. Increased thrombosis of catheters or extracorporeal filters during CRRT has been recognized and specific anticoagulation protocols have been developed to mitigate the hypercoagulable state.[21]

PROGNOSIS OF COVID-19 PATIENTS WITH AKI

AKI has a major impact on survival among hospitalized COVID-19 patients (**Table 1**). In a large cohort from New York, in-hospital mortality among patients with AKI was 41%, the rate increased to 52% in those admitted into intensive care with AKI.[7] The adjusted odds ratio for mortality associated with AKI was 9 overall and 20.9 in patients receiving intensive care.

In another cohort from New York, among 1,993 patients who developed AKI during the hospitalization, 26% of patients were discharged and 35% died.[6] Of those with AKI, risk of death and prolonged hospital stay was related to severity of AKI: 57% with stage 1 AKI died or were still hospitalized during the study period as compared with 80% with stage 2 and 94% with stage 3. Among the 285 patients who required RRT, 157 died and only 9 were discharged from the hospital. Another 119 were still undergoing treatment in the hospital, with 108 still on RRT (90.8%).

Outside United States, Cheng et al examined 701 hospitalized COVID-19 patients in Wuhan, China, and found AKI carried a significantly increased risk for in-hospital mortality.[4] Cox proportional hazard regression confirmed that baseline CKD, AKI, proteinuria and hematuria were all independent risk factors for in-hospital death after adjusting for age, sex, disease severity, comorbidity and leukocyte count. Therefore, both baseline CKD and AKI during hospitalization in patients with COVID-19 is clearly associated with higher in-hospital mortality.

CONCLUSION AND FUTURE PERSPECTIVES

The COVID-19 pandemic is far from over with millions of cases reported worldwide, and over 200,000 new cases reported daily.[1] The pathogenesis of AKI has not been clearly established in this patient population. The therapeutic responses of patients with AKI to various medications under clinical investigation are unclear. The impact of AKI on disease duration, viral clearance, risk of CKD and long-term survival are also uncertain. As the healthcare system and resources become overwhelmed by COVID-19 pandemic, the access to routine CKD care and kidney transplantation can be negatively affected and its short-term and long-term impact warrants further investigation. Lastly, an evidence-based comprehensive management guideline is desperately needed to win this battle.

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