COVID-19 Pandemic and the Burden of Acute Kidney Injury: The Known and the Unknown

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ABSTRACT

The present pandemic of severe acute respiratory syndrome (SARS) is caused by a novel enveloped RNA β-coronavirus (2019-nCoV), commonly called COVID-19. Starting from China, it has spread worldwide, causing major morbidity and mortality. It primarily involves the pulmonary system, but other organ systems are not spared. Treatment is still elusive and evolving. The exact pathogenesis of renal damage from COVID-19 virus and the magnitude of renal failure in this infection are not very clear. PubMed was searched to identify published literature from 2019 to present using the following keywords: COVID-19, acute kidney injury, creatinine, blood urea nitrogen, chronic kidney disease, renal replacement therapy, and dialysis. Cited references were also used to further identify relevant articles and literature elsewhere on the web. This review looks at the burden and influence of the COVID-19 pandemic on the kidneys and on the implications it will have on public health planning.

INTRODUCTION

The present pandemic of severe acute respiratory syndrome (SARS) is caused by a novel enveloped RNA β-coronavirus (2019-nCoV), commonly called COVID-19. It has spread from China to the rest of the world with human-to-human transmission. Major morbidity and mortality issues from this virus are caused by involvement of the pulmonary system.1

In the largest published study of 1099 patients from China, the median incubation period was 4 days (interquartile range [IQR] = 2-9), and median patient age was 47 years (IQR = 35-58). The most common symptoms at admission were fever (37.5°C or higher) in 43.8% patients and cough in 67.8% of patients. At admission, ground glass opacity was the most common radiologic finding on computed tomography (56.4% of patients), and lymphocytopenia (lymphocyte count of < 1500 cells per cubic millimeter) was most common (83.2% patients). A total of 27% patients had at least 1 coexisting illness (eg, hypertension, chronic obstructive pulmonary disease).2 Patients with more severe disease had a higher incidence of physician-diagnosed pneumonia and more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with nonsyndrome disease. Five percent were admitted to the intensive care unit (ICU).2 In another short series from China, the overall mortality rate in COVID-19 cases was 4.3% among 138 hospitalized patients.3

The current reported case fatality rate was approximately 6% globally as of April 11, 2020, per a World Health Organization COVID-19 situation report.4 Guan et al2 reported mortality of 1.4% among diagnosed symptomatic patients. Among the first 140,904 cases reported in the US, about 1.7% died. However, due to unclear denominator numbers, the reliability of that rate is questionable.5 Subsequent analysis by Johns Hopkins University Coronavirus resource center shows that, as of April 29, 2020, the observed case/fatality ratio (ie, number of deaths either per 100 confirmed cases) was 5.8% in the US.

Although diffuse alveolar damage is the major feature of this disease, the involvement of many other organ systems has been reported. Here we review the influence of the burden of acute kidney injury of (AKI) in the COVID-19 pandemic.

Incidence of AKI

Among the earliest reports coming from China, out of 116 hospitalized patients without chronic kidney disease (CKD), 10.8% showed only a mild increase (< 26 µmol/L or 0.3 mg/dL) in serum creatinine (Cr) and did not meet the criteria for AKI based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines.6 Another study also did not show an impressive rate, with only 6 (0.5%) patients developing AKI out of 1099 patients.2

However, subsequent studies have shown higher incidences of AKI. AKI (diagnosed according to KDIGO clinical practice guidelines) seems to develop at a median of 15 days (IQR = 13-19.5 days), and AKI occurred in 15% of patients out of total of 191 admitted patients.7 In a study of 41 admitted patients, the incidence of AKI (according to KDIGO) was 7% overall (3 out of 41 patients). All 3 of these patients were in the ICU.8 In another short series from China, the incidence of AKI (defined per KDIGO guidelines) in COVID-19 cases was 3.6% in 138 hospitalized patients. Of a total of 5 patients who developed AKI, 3 were in the ICU.9 Another study of 85 admitted patients reported a 27.06% incidence of AKI. In patients with hypertension and heart failure, the incidence was much higher (65.22% vs 24.19% and 69.57% vs 11.29%, respectively).3 A study of 193 patients found that at the time of admission 60% had...
proteinuria and 48% had hematuria (measured from semi-quantitative urinalysis).10

In a large prospective cohort study of 701 adult patents from Wuhan, 5.1% had AKI (based on KDIGO guidelines). About 44% had proteinuria at admission (not quantified), and 27% had hematuria, but some had Foley. They did not clarify if the proteinuria and hematuria were new and due to AKI or were due to the baseline CKD because no baseline prehospitalization data were noted. Coagulation pathway abnormalities, procalcitonin, aspartate aminotransferase, and lactose dehydrogenase were higher in patients with elevated baseline Cr. Cr kinase was not significantly elevated. Incidence of AKI during hospitalization was higher in those with elevated baseline Cr than in those with normal baseline Cr (11.9% vs 4%). Compared with normal baseline Cr, patients with elevated baseline Cr were more likely to undergo mechanical ventilation (12.5 vs 21.8%, p = 0.012).11 A study of 710 patients in Wuhan looked at 52 (7.3%) critically ill patients admitted to the ICU. None of them was reported to have baseline chronic renal disease. Fifteen (29%) patients developed AKI based on the elevated Cr.12

Earlier reports from Italy showed an AKI incidence as high as 15%.13 Detailed reports of AKI from the US are not yet available. In a study of 21 ICU patients, 11 patients (52.4%) died. Among those 21 patients, 4 patients (19.1%) developed AKI.14

AKI and Mortality

Development of AKI in COVID-19-positive patients has been shown to portend worse survival. Incidence of in-hospital death was 33.7% with higher baseline Cr (132 ± 39 µmol/L) as compared with 13.2% with normal baseline Cr (68 ± 16 µmol/L). Higher AKI stages were independent risk factors for mortality in the multivariable model.15 In the Zhou et al7 study of 191 patients, 28 patients had AKI. In another study, among 99 inpatients, 23 were admitted to the ICU; 9 of these patients required RRT.15 A detailed report was compiled by the Intensive Care National Audit and Research Center, which reports data on confirmed critically ill COVID-19 cases in England, Wales, and Northern Ireland. The last report from April 9, 2020 was reviewed. Prior to admit, only 1.9% of 1053 patients requiring advanced respiratory support (invasive ventilation) were on RRT for end-stage renal disease. Of these patients, 26.3% required renal support (acute RRT). In comparison, among the 444 patients who received only basic respiratory support, only 2.9% required renal support.16 No such detailed published reports are available from the US as of now.

Etiology of AKI

The exact mechanism as to how this virus accesses the kidney is unclear. Angiotensin- converting enzyme 2 (ACE2), an enzyme that physiologically counters the renin–angiotensin–aldosterone (RAAS), is the functional receptor to COVID-19 virus.17 It has been shown that the virus binds with ACE2, which is well expressed in the podocytes and proximal tubular epithelial cells per single-cell RNA sequencing data. It was noted that podocytes and proximal tubular epithelial cells were potential target hosts for this virus.18 In cases of worsening pneumonia and shock, the maladaptive systemic inflammatory response with the cytokine storm likely further contributes to renal tubular injury.19 Although select preclinical studies have suggested RAAS inhibitors may increase ACE2 expression, insufficient data are available to evaluate the safety and effects of RAAS inhibitors in treating patients with COVID-19.17

The few reports available are contradictory regarding whether COVID-19 directly invades the kidney and if it acts through direct cytopathic effects on the kidney. Su et al18 analyzed 26 autopsies of COVID-19 patients. Light microscopy showed diffuse proximal tubule injury and frank necrosis. There were occasional hemosiderin granules and pigmented casts. Erythrocyte aggregates without platelet or fibrinoid material were noted in capillaries. There was no evidence of vasculitis or interstitial inflammation. Electron microscopy (EM) showed coronavirus particles in tubular epithelium and podocytes.21

In another study, kidney tissue from 6 patients was analyzed postmortem. Hematoxylin and eosin staining demonstrated severe acute tubular necrosis and lymphocyte infiltration. Immunohistochemistry showed SARS-CoV-2 nuclear protein antigen accumulation in kidney tubules. Two samples had...
EM; virus-like particles 80-160 nm in diameter were observed in broken lysosomes. Doing further immunohistochemistry, the authors noted that viral infection not only induces CD68+ macrophages infiltrated into tubulo-interstitial but also enhances complement C5b–9 deposition on tubules, further causing tubular pathogenesis. A biopsy on a single black COVID-19-positive patient showed severe collapsing focal segmental glomerulosclerosis and acute tubular necrosis. EM showed spherical particles resembling viral inclusion bodies.

However, another recent case report did not show viral particles. Larsen et al reported another COVID-19-positive black patient with APOL1 genotype who rapidly developed AKI requiring RRT and remained dialysis dependent. The biopsy findings revealed 24 glomeruli, but 14 were globally sclerotic, whereas others showed tuft collapse. There was proximal interstitial inflammation with lymphocytes and plasma cells. Interstitial fibrosis and tubular atrophy were moderate. Immunofluorescence was negative. Ninety percent of glomerular basement membrane showed foot process effacement. No definitive viral particles were identified by EM. In situ analysis for the presence of SARS-CoV-2 RNA did not show evidence of viral RNA (it was performed using an RNA scope). The authors noted that the collapsing glomerulopathy may have been unrelated to the viral infection and was only brought to attention by this infection. It is very likely that more cases of APOL–1-related collapsing glomerulopathy leading to long-term RRT in patients who have recovered from COVID-19 will be showing up in African American communities.

Reports of viral presence in urine have been inconsistent. Guan et al noted the presence of the virus in the urine of 1 patient (Supplemental Table 2a), although it is not clear how many urine specimens were tested. SARS-CoV-2 RNA in urine sediments was reportedly positive only in 3 patients from many urine specimens were tested. SARS-CoV-2 RNA in 1 patient (Supplemental Table 2a), although it is not clear how interventions are needed in these critical patients. All these interventions create a heavy burden on any health care system. AKI may be the next emerging healthcare and resource issue in this pandemic. Anecdotal reports of a high incidence of patients needing RRT in ICU and centers running short of dialysis equipment are alarming. Short-term and long-term damage to kidneys will be a major sequela of this pandemic. More and more of the recovering COVID-19 patients might end up on long-term dialysis.

More broad-based studies are required to analyze the incidence of AKI in these COVID-19-positive cases. Knowing the burden of AKI in this pandemic is vital for overall planning by public health officials. This will help plan for equipment and staff needed for potential short-term and long-term RRTs. Meanwhile, preventing AKI in COVID-19-positive patients should be a part of comprehensive care in ICU through regular monitoring, prompt diagnosis, and timely intervention.

Overall, the data on AKI in COVID-19-infected patients are not very robust. Many reports are small case series, and some are not peer reviewed. Although effective proven therapy remains elusive and continues to evolve, many other interventions are needed in these critical patients.

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Supplemental Material

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