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Review Article

Kidney disease in the coronavirus disease-2019 pandemic

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Abstract

While Coronavirus disease-2019 (COVID-19) is primarily a respiratory tract infection in most cases of mild to moderate disease, severe disease can involve multi-organ failure including acute kidney injury (AKI). COVID-19-associated AKI may require renal replacement therapy (RRT) in the acute setting or chronically after hospital discharge. The COVID-19 pandemic presented considerable difficulties to the nephrology community, requiring epidemiologic, clinical, and pathologic studies of AKI associated with the acute phase of infection. In this review article, AKI studies, pathologic entities, and specific adaptations to RRT will be discussed.

Key words: Acute kidney injury, Collapsing glomerulopathy, Coronavirus disease-2019, Renal replacement therapy

Introduction

"Coronavirus disease-2019" (COVID-19) emerged as an infectious disease in late 2019 that began as an outbreak in Wuhan, China. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic viral strain causing COVID-19, a clinical syndrome of primary pneumonia and respiratory failure with a secondary hyperinflammatory syndrome, cytokine dysregulation, and other effects. COVID-19 has a 1–2 week asymptomatic incubation period with a low likelihood of a positive diagnostic assay.[1] After respiratory symptom onset, the virus can be isolated from samples obtained from nasopharyngeal swab and detected by polymerase chain reaction (PCR) assay up to 3–4 weeks post-infection. Bronchoalveolar lavage PCR and stool PCR remain positive for SARS-CoV-2 up to 4 and after 6 weeks post-infection, respectively. IgM is detectable by serologic testing from 10 days to 6 weeks post-infection, and IgG is durably detectable post-infection.

As of April 2021, there have been over 148 million COVID-19 cases worldwide and over 3.1 million deaths. Within the United States there have been 32.1 million cases with over 572,000 deaths. One meta-analysis of 2486 patients from five countries found that among hospitalized patients with COVID-19 pneumonia, 33% developed acute respiratory distress syndrome (ARDS), 26% required intensive care unit (ICU) care, and 16% required ventilator support.[2] Among ICU patients, 63% required ventilator support, 75% developed ARDS, and there was a 45% mortality rate. ARDS was 90% prevalent among the fatalities as determined by postmortem lung examination revealing diffuse alveolar damage.

Extrapulmonary Targets of Infection

While primary SARS-CoV-2 infection follows droplet and airborne transmission through the respiratory route, patients with COVID-19 pneumonia and secondary hyperinflammatory syndrome have been reported to have extrapulmonary complications. Symptoms and findings include neurological (headaches, encephalopathy, Guillain-Barre syndrome, and stroke), cardiac (acute cardiomyopathy, myocarditis, arrhythmias, and acute cor pulmonale), renal (acute kidney injury [AKI], proteinuria, and hematuria), hepatic (elevated transaminases and bilirubin), gastrointestinal (nausea, vomiting, abdominal pain, and diarrhea), hematologic (deep venous thrombosis, pulmonary embolism, and intravascular catheter-associated thrombosis), and dermatologic (livedo reticularis, urticaria, vesicles, and lupus pernio-like lesions).[3,4] Furthermore,

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thrombotic disorders have been described in multiple organ systems, including cerebral venous sinus thrombosis, renal infarction, portal venous thrombosis, and mesenteric vessel thrombosis.[5,6] These events have been linked to anti-phospholipid antibodies in observational studies.[7,8]

AKI Prevalence

Early international reports from China, Europe, and the United Kingdom showed wide-ranging AKI prevalence from 0.5% to 46%. Furthermore, Chinese studies did not report prevalence of chronic kidney disease (CKD), a major AKI risk factor, among those with incident AKI.[9] Later European and US reports indicated a greater burden of comorbid conditions than early reports, with higher rates of AKI.

One cooperative study of populations of New Orleans and three New York systems specifically assessed AKI and outcomes at 5–7 weeks post-infection.[9] AKI risk factors of male sex, African American race, and age over 50 years were identified. CKD and hyperkalemia were independent predictors of KDIGO Stage III AKI. There were higher rates of AKI and requirement of renal replacement therapy (RRT) in patients with COVID-19 versus matched historical control patients within the same hospitals. Patients with AKI were more likely to require ICU admission, require ventilator support, and vasopressors. Furthermore, 90% of ventilated COVID-19 patients versus 22% of non-ventilated COVID-19 patients exhibited AKI. COVID-19 patients with AKI also had significantly higher levels of inflammatory markers ferritin, d-dimer, C-reactive protein, lactate dehydrogenase, and procalcitonin. COVID-19 patients with AKI exhibited increased in-hospital mortality compared to COVID-19 patients without AKI (45% vs. 7%). In the ICU, 52% of COVID-19 patients with AKI had in-hospital mortality compared to 9% of patients without. AKI was associated with significant risk for in-hospital mortality, with 37.5 deaths per 1000 patient-days among AKI patients versus 10.8 deaths per 1000 patient-days among non-AKI patients. Forty-three percent of patients with AKI had abnormal kidney function at time of hospital discharge.

The STOP-COVID group of investigators in the United States began a multi-center collaborative study in March 2020 that enrolled over 5000 patients with COVID-19 admitted to ICUs at 68 centers. Descriptive and laboratory data were entered into an online database for statistical analysis. An initial study identified a 28-day mortality rate of 35.4% among 2215 critically ill patients.[10] Mortality risk factors included male sex, age, obesity, coronary disease, acute organ dysfunction, and admission to a hospital with fewer than 50 ICU beds, which carried over three-fold increase in mortality risk. There was a 30% lower risk of mortality in a subgroup of 384 (11%) patients treated with tocilizumab versus those receiving protocolized care (n = 3491). In a subgroup analysis done according to the presence of CKD (n = 521) and patients receiving chronic dialysis (n = 143) before hospital admission for COVID-19, compared to control patients without kidney disease, mortality rates were found to be 50% (HR 1.41), 51% (HR 1.25), and 35%, respectively. Chronic dialysis patients were found to exhibit more rapid progression of symptoms requiring ICU admission relative to control group patients, and they were more likely to present with metabolic encephalopathy at the time of admission. In a later analysis, investigators performed logistic regression to identify risk factors for AKI-RRT.[11] The determined risk factors were baseline CKD, male sex, non-white race, obesity, severe ARDS, and higher d-dimer level. Among the study population (n = 3099), 21% of patients developed AKI-RRT, 63% of AKI-RRT patients died in the hospital, and 34% of survivors of the index hospital admission remained dialysis-dependent on hospital discharge. About one in six patients were still dialysis-dependent 60 days after ICU admission.

AKI Mechanisms

The etiology of AKI during acute illness with COVID-19 is multifactorial. There is proven parenchymal viral infection of the kidney, which can manifest as rare primary glomerular disease, such as collapsing glomerulopathy, thrombotic microangiopathy (TMA), minimal change disease, profound proximal tubular injury, and necrosis. Superimposed on direct cytopathic effects are systemic factors due to critical illness, including sepsis, hypotension, hyperperfusion, arrhythmias, hypoxia, viral myositis, and rhabdomyolysis as well as nephrotoxic exposures such as intravenous contrast, vancomycin, and other antimicrobial agents [Figure 1].[12]

Direct viral entry of SARS-COV-2 into renal parenchymal cells is mediated by viral S-protein binding the angiotensin-converting enzyme 2 (ACE-2) receptor.[13] In renal tissue, ACE-2 expression is greatest in the proximal convoluted tubule. The viral S-protein is cleaved by host cellular transmembrane proteases (e.g., TMPRSS2 in the distal convoluted tubule) which permit ACE-2 recognition. There are postulated to be other proteases in the proximal convoluted tubule where viral mediated injury is more pronounced.[13]

This viral pathway of cell entry fostered two hypotheses of how renin-angiotensin-aldosterone system (RAAS) inhibition may have a role in the propagation of viral cytopathic injury to renal cells.[14] In the first hypothesis, RAAS inhibitor use increases ACE-2 abundance on the renocyte surface, enhances viral entry, and has a harmful effect. In the second hypothesis, reduced concentrations of angiotensin II and reduced angiotensin II type 1 receptor activation enhances Mas receptor activation, leading to attenuation of inflammation and fibrosis in tissues expressing ACE-2. These hypotheses were examined in the BRACE CORONA trial, which enrolled patients (n = 659) at 29 sites in Brazil with a mean age of 56 years.[15] Investigators found no difference in outcomes in patients who were maintained on RAAS inhibitors (n = 334) versus patients stopping RAAS inhibitor use (n = 325) for 30 days following a COVID-19 diagnosis. There was no significant difference in the primary endpoint of patient life-days and hospitalization-free days.

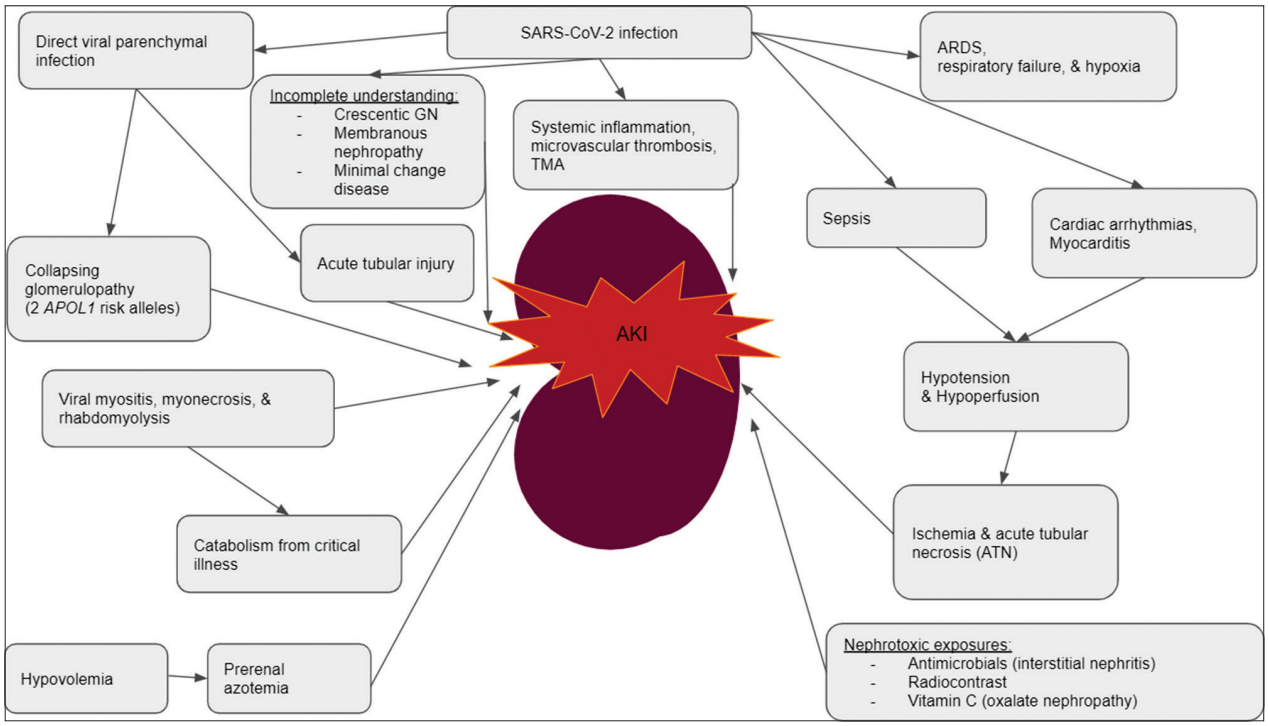

Figure 1: Direct (virally mediated) and indirect mechanisms of AKI in COVID-19

Secondary endpoints including all-cause mortality difference at 30 days, rates of myocardial infarction, stroke, and disease progression were also not significantly different between groups. A potential limitation of the study was the relatively young study population and the short period of study.

Pathologic Reports

Pathological reports provided insight into the COVID-19-associated AKI and urinary abnormalities. One of the largest series of postmortem examinations of Wuhan patients who died of COVID-19 included 26 patients.[16] In this study, the average age of deceased patients was 69 years. The patients died of respiratory failure and multi-organ failure. Nine patients (34%) had laboratory testing showing clinical kidney injury, including elevated serum creatinine, and urinalysis showing hematuria, proteinuria, and pyuria in varying severity. All patients were confirmed COVID-19-positive by nucleic acid amplification tests and had typical lung imaging. Eleven patients had past histories of hypertension, diabetes, or both. Light microscopy showed tubular necrosis with loss of the brush border, vacuolar degeneration, necrotic epithelia, and inflammatory infiltrates in the tubules and arterioles. Some biopsies also showed erythrocyte aggregation and obstruction in capillary loops without distinct TMA or fibrin thrombi. Electron microscopy showed purported viral particles in the cytoplasm of tubular cells and podocytes, but this was disputed in letters with other authors demonstrating that they were more consistent with clathrin-coated vesicles, an endogenous structure, and cellular transport mechanism.[17] One patient with historical IgA nephropathy had electron microscopic evidence of relapsing disease. A common finding among many of the biopsies was erythrocyte aggregation and varying degrees of endothelial injury. Two-thirds of patients had characteristic changes associated with diabetic nephropathy on electron microscopy. Immunohistochemistry staining showed nonspecific scarring with lymphocytic infiltrates and occasional macrophages. CD235a-positive staining was used to positively demonstrate erythrocyte obstruction. Immunofluorescence demonstrated altered ACE-2 patterns with enhanced prominence in the proximal tubules relative to control biopsies, particularly those with severe tubular injury. Indirect immunofluorescence for SARS-CoV-2 nucleoprotein showed tubular inclusions, with three out of six cases showing a granular pattern of staining in the nucleus or cytoplasmic distribution in the tubular epithelia.

Several independent case reports established the occurrence of collapsing glomerulopathy in patients with COVID-19.[18-21] These patients reportedly had severe AKI with heavy proteinuria, with later onset than the pulmonary and systemic disease course. Biopsies revealed severe collapsing glomerulopathy, prominent tubular injury, diffuse podocyte effacement, and the presence of endothelial tubuloreticular inclusions.[21] One patient had renal recovery after respiratory recovery, and two patients remained dialysis-dependent at time of hospital discharge. The occurrence of primary glomerulopathy was ascertained to be a direct viral effect in one patient and be a cytokine effect in two patients.

All patients were of Sub-Saharan African descent and two patients tested carried renal risk alleles for *APOL1*. A pathogenic explanation for collapsing glomerulopathy is that SARS-CoV-2 infection may be a "second hit" in individuals harboring *APOL1* risk alleles, leading to podocyte dysregulation and injury.[22]

Challenges and Adaptations to RRT

RRT in the inpatient setting faced challenges during the COVID-19 pandemic. As COVID-19 patients developed the secondary hyperinflammatory phase of the disease, clotting of the dialysis filter became a problematic and often recurrent issue.[23] Centers developed and reported their own protocols for monitoring the severity of coagulopathy and thrombotic diathesis with d-dimer and anti-Xa levels.[24] Full-dose therapeutic intravenous heparin emerged as the ideal anticoagulant for patients with COVID-19-associated coagulopathy.[25]

Concerning continuous RRT (CRRT) in particular, the proprietary AN69 filter Baxter Oxiris received an FDA Emergency Use Authorization (EUA). The terms of the EUA permit the filter to be selected for use for COVID-19 patients who have early acute lung injury or clinical ARDS and concomitant life-threatening disease, including septic shock, multiple organ dysfunction, and/or organ failure.[26] The filter has a novel three-layer membrane structure with a heparin-grafted membrane to reduce thrombogenicity, a polyethyleneimine surface treatment for endotoxin adsorption, and an enhanced AN69 membrane for cytokine adsorption. Available data suggest that the Oxiris filter may reduce the number of filter-related complications in patients with COVID-19.[27]

In addition to disease-related challenges, staffing and technical challenges surrounding CRRT in the ICU also emerged. Due to supply deficits in personal protective equipment (PPE), strategies to conserve PPE became essential. Some centers implemented dialysis extension tubing to locate the dialysis machine outside of the patient's room so that machine alarms and adjustments could be addressed by the staff or technician without them donning PPE. This also reduced some of the burden of machine disinfection between treatments on different patients. Many centers also adopted styles or implemented policies on selection of RRT modality and time use for treatments.[28] Examples include running CRRT for 12 h per patient per day if appropriate according to the individual goal for fluid balance and delivered clearance, and selection of prolonged intermittent RRT as the modality for patients with intermediate hemodynamic (in)stability.

Acute peritoneal dialysis (PD) for end-stage renal disease (ESRD) and AKI patients with COVID-19 was protocolized at some epidemic centers where medical need was above capacity.[29] Recipients were ESRD-PD patients or AKI patients initiated on acute PD as salvage therapy after CRRT clotting, or as the primary modality of RRT due to limited capacity. Acute PD is not the ideal modality in patients with active abdominal pathology, recent abdominal surgery, severe hyperkalemia, or increased intra-abdominal pressure. Acute PD requires the placement of a peritoneal catheter either at the bedside or laparoscopically. Patients intended to begin acute PD as the modality for RRT are recommended to be initiated strategically before the development of metabolic or fluid-related emergencies.

Conclusion

COVID-19 has been recognized not only as a respiratory disease, but also for its extrapulmonary effects. COVID-19 patients can present with severe AKI that requires intermittent dialysis or CRRT. The prevalent AKI phenotype in COVID-19 patients is ischemic tubular injury, although more rare primary glomerular presentations, including collapsing glomerulopathy, have been reported. Renal injury is linked to direct SARS-CoV-2 infection of the kidney parenchyma via the ACE-2 receptor. However, adverse outcomes were comparable among patients continuing or suspending use of RAAS inhibitors during hospital admission for acute COVID-19, indicating that blockade of the ACE-2 inhibitor in the kidney is not related to more severe forms of COVID-19. Nephrologists have faced several inpatient RRT challenges during the COVID-19 pandemic. These challenges require consultants and centers to rapidly adapt RRT protocols as well as to adeptly solve staffing and technical issues related to caring for COVID-19 patients with AKI.

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