

Acute Kidney Injury in the Time of COVID-19

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“Wisdom comes to us when it can no longer do any good”. Gabriel García Márquez, in *Love in the Time of Cholera*

Respiratory Disease, Respiratory Failure, and Ventilator Shortages

Those were the concerns in late February and early March, shortly before the surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) hit the United States. By late March, not only were intensive care unit beds full and respiratory failure rampant in some major cities in the United States, but there was a new enemy lurking. The tsunami started to hit. It was not volume depletion-induced serum creatinine elevations. It was severe AKI with multiple electrolyte derangements. Troops were summoned and dialysis nurses worked around the clock to try to provide clearance to patients all over hospitals. Four-hour dialysis treatments were a thing of the past; 2 hours sometimes had to suffice. While President Trump enacted the Defense Production Act to force companies to make more ventilators, kidneys and life-sustaining dialysis machines were the forgotten resources.

How did this happen? By the beginning of June, over 6.9 million patients had been diagnosed worldwide and more than 400,000 people had died. However, the early reports from China noted a relatively low incidence of AKI, some as low as 0.5%, with most studies reporting cumulative incidence in the single digits to the teens (1).

Thus, the United States was not expecting an onslaught with regard to kidney disease

Now that the initial wave of the pandemic has passed, five studies from centers in the United States have come out documenting a much higher proportion (19%–43%) of AKI in hospitalized patients with COVID-19 (Table 1).

One of the United States-based studies documented experiences with AKI of hospitalized patients with COVID-19 at the Ochsner Health System in New Orleans (2). The overall incidence of AKI in this cohort was 28%, which aligns with the other United States-based reports (Table 1). Over one half of patients with AKI required acute dialysis; 98% of these patients received sustained low efficiency dialysis, and only two patients never required prolonged intermittent renal replacement therapy or continuous renal replacement

therapy. These findings highlight how truly sick patients with COVID-19 were. Unique features of this study from Mohamed *et al.* are that the majority (71%) of the cohort were black and the authors performed manual chart reviews in an effort to ascertain the causes of AKI. As we and likely others have seen, many patients with severe AKI eventually made comfort care or died before RRT initiation. Whereas most papers consider this as “never having received dialysis,” in their paper Mohamed *et al.* classified these patients as “patients who died with a rising serum creatinine and oliguria” and chose to treat them as if they had required RRT. This subpopulation accounted for 21.6% of the total number of RRT patients. This unique characterization likely reduces information bias (informative censoring of the outcome of interest due to the competing risk of death or comfort care), and should be considered when comparing the incidence of severe dialysis-requiring AKI with other studies on AKI and COVID-19.

The authors should also be commended on their manual chart review of medical records and notes of >600 patients to identify the causes of AKI. Through their chart review, the authors found that 66% of patients had acute tubular injury. Urinalysis revealed a large proportion of patients with 2+ proteinuria overall (69%) of which 39% were found to be *de novo* proteinuria. Moreover, 69% had hematuria of which 19% was 2+ or ≥ 8 red blood cells/hpf. Unfortunately, this study did not report urinalysis findings in patients without AKI. A small portion of the cohort had urinary sediment microscopy performed; additional details of the urine sediment were published in a separate paper (3). The second study from the Oschner investigators is, to date, the only study in the United States to have reported urine sediment in patients with COVID-19 and AKI. Hopefully, as the potential risks of SARS-CoV-2 infectivity in urine become better understood, more urinary sediment evaluation will be performed and reported, given its diagnostic value.

Three patients underwent percutaneous kidney biopsy, of which all had collapsing glomerulopathy. This histopathologic finding has been reported in several case reports of patients with COVID-19 and AKI. Given that the majority of patients were black, it would be of interest to know the proportion of patients in this cohort that had the high-risk *APOL1* genotype, given the association between *APOL1* and development of collapsing FSGS in patients with and without HIV. *Postmortem* studies of kidney tissue report detection of

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Table 1. Reported incidence of AKI and need for RRT in United States centers

Center ^a	Paper	Study Population	<i>n</i> and Proportion with AKI ^b	Need for RRT
Northwell Health System	Hirsch <i>et al.</i> (8)	New York hospitalized (<i>N</i> =5449)	1993 (37%)	285 (5%)
Mount Sinai Health System	Chan <i>et al.</i> (9)	New York hospitalized (<i>N</i> =3235)	1406 (43%)	280 (20%)
Columbia	Cummings <i>et al.</i> (5)	New York critically ill (<i>N</i> =257)	NR	79 (31%)
Oschner Health	Argenziano <i>et al.</i> (10)	New York hospitalized (<i>N</i> =1000)	288 (33%)	117 (13.8%)
	Mohamed <i>et al.</i> (2)	New Orleans hospitalized (<i>N</i> =575)	161 (28%)	89 (15%)

NR, not recorded.
^aStudies of 100 patients or more.
^bCreatinine rise ≥ 0.3 mg/dl or 50% rise from baseline.

virus in the kidney tubular epithelium and podocytes (4). However, these patients are likely to have had the most severe cases of COVID-19 and, so far, there has been no detection of SAR-CoV-2 in kidney biopsies.

Why do the studies from China have such differing incidence and outcomes of AKI compared with those in the United States? One potential reason may be related to the much higher burden of reported comorbidities in the United States cohorts compared with the Chinese cohorts (Figure 1) (1,2,5). Many of these comorbidities have been associated with worse outcomes in hospitalized patients with COVID-19. Additionally, there may be differences in angiotensin-converting enzyme 2 expression between Asians and occidental persons in various nephron segments, including the proximal tubules, which may explain the increased risk for AKI with SARS-CoV-2 in non-Asians (6). As more reports from other countries come out, it is becoming clearer that there are indeed regional differences in the incidence of AKI, with a study from France reporting that 80% of hospitalized patients developed AKI (7). Although there are nearly 2 million confirmed cases of COVID-19 in the United States alone, data regarding kidney outcomes have only emerged from limited sites thus far (Table 1). To truly understand the epidemiology of kidney disease in patients affected by COVID-19, we will need analyses across different health systems representing

heterogeneous people of varied racial, ethnic, and cultural makeup, and health systems with different levels of resources and surge capacity. One such observational study, involving 60 sites across the United States, is currently underway [Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) NCT04343898] and may shed some light on regional differences across the United States.

Although much remains to be elucidated about the novel SARS-CoV-2, we need to take a step back to review how much has been achieved in a very short period of time. During the early 1980s, the United States was hit by the AIDS epidemic. It took 2 years to identify the virus, and the first reports of HIV-associated nephropathy were 3 years into the epidemic. The World Health Organization was first notified of COVID-19 on December 31, 2019. The full genetic sequence of SARS-CoV-2 was publicly shared by China on January 12, 2020. Within a 6-month time span we have had numerous epidemiologic studies, several ongoing therapeutic clinical trials, and clinical trials have already begun for potential vaccines. The speed at which these things are being achieved for SARS-CoV-2 is a testament to the progress that science has made in the past few decades.

Now that the surge has quieted in many segments of the United States, the next few months will be a critical time in which to expand the investigations into COVID-19

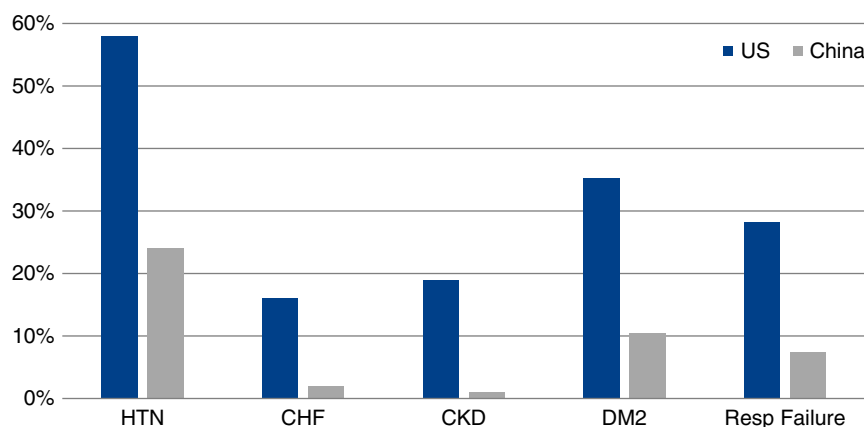


Figure 1. | Proportion of reported comorbidities in studies from China and the United States. Adapted from Coca *et al.* (1) and updated with the United States studies listed in Table 1. HTN, hypertension; CHF, congestive heart failure; DM2, type 2 diabetes; Resp, respiratory.

and the kidneys. As the country sets to reopen the economy despite a lack of widespread immunity, and with an effective vaccine months away, it is likely only a matter of months before wave 2. Thus, we disagree with Gabriel García Márquez that “wisdom comes to us when it can no longer do any good.” We have the opportunity to apply insights gained from the first wave to help us manage and triage patients with COVID-19 during the next wave, or a continued plateau that may last for several months. Some critical questions to answer include the following:

- (1) What is the incidence of AKI and dialysis during nonsurge conditions in patients admitted with COVID-19?
- (2) What is the risk of AKI to CKD transition after COVID-19 (*i.e.*, what proportion of patients will develop incident or progressive CKD after initial hospitalization with AKI)?
- (3) Due to the high incidence of acute tubular injury in patients without clinical AKI (4), what will be the risk for CKD in COVID-19 survivors that experienced “sub-clinical AKI?”
- (4) What are the early predictors of both acute and severe AKI, and what are the predictors of nonrecovery and long-term CKD in patients with COVID-19?
- (5) What management strategies can be implemented to decrease the risk of both acute and chronic kidney outcomes?
- (6) What proportion of patients will have long-lasting proteinuric kidney disease, by involvement of SARS-CoV-2 in podocytes or through “second-hits” in patients with an underlying *APOL1* genotype?

Clinical investigators can take this summer reprieve and build up the infrastructure and data pipelines to try to inform the nephrology community, and the population at large, about the full landscape of COVID-19 kidney disease. We owe it to humanity to be better prepared against this devastating viral pandemic.

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Author Contributions

Both authors were responsible for conceptualization, writing the original draft, and reviewing and editing the manuscript.

Disclosures

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