Acute Kidney Injury in the time of COVID-19

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Respiratory disease. Respiratory failure. Ventilator shortages.

Those were the concerns in late February and early March, shortly before the surge of SARS-CoV2 and COVID-19 hit the United States. By late March, not only were ICUs 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 wasn't 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; two hours sometimes had to suffice. While President Trump enacted the Defense Production Act to force companies to make more ventilators, the kidneys and the life-sustained dialysis machines were the forgotten resource.

How did this happen? By the beginning of June, over 6.9 million cases have been diagnosed worldwide and more than 400,000 have died. However, the early cases from China reported 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 US was not expecting the onslaught in regards 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).
One of the US-based studies documented the experiences with AKI in hospitalized patients with COVID-19 at the Ochsner Health System in New Orleans. The overall incidence of AKI in this cohort was 28%, which aligns with the other US-based reports (Table). Over half of patients with AKI required acute dialysis; 98% of these patients received sustained low efficiency dialysis, and only 2 patients never required PIRRT or CRRT. These findings highlight how truly sick patients with COVID-19 were. Unique features of this study from Drs. Mohamed, Velez, and colleagues are that a majority (71%) of the cohort was Black and the authors performed manual chart review in an effort to ascertain the etiology of AKI. As we and likely others have seen, many patients with severe AKI were eventually made comfort care or died prior to RRT initiation. While most papers consider this as “never having received dialysis”, in this paper the authors classified these patients as “patients who died with a rising serum creatinine and oliguria (DWRCO)” and chose to treat them as if they had required RRT. This subpopulation accounted for 21.6% of the total 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 on >600 patients to identify etiology of AKI. Through their chart review, the authors found that 66% of cases were from acute tubular injury (ATI). 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 RBC/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 was published in a separate paper. The second study from the Oschner investigators is, to date, the only study in the US to have reported urine sediment in patients with COVID-19 and AKI.
Hopefully as the potential risks of SARS-CoV-2 infectivity in urine is 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 the majority of patients were Black, it would be of interest to know the proportion of patients in this cohort who had APOL-1 high risk genotype given the association between APOL1 and development of collapsing FSGS in HIV and non-HIV patients. Post mortem studies of kidney tissue report detection of virus in the kidney tubular epithelium and podocytes. However, these cases are likely to be the most severe cases of COVID-19 and so far there has been no detection of SAR-CoV-2 on kidney biopsy.

Why do the studies from China have such differing incidence and outcomes of AKI compared to those in the US? One potential reason may be related to the much higher burden of reported comorbidities in the US cohorts compared to the Chinese cohorts (Figure). Many of these comorbidities have been associated with worse outcome in hospitalized patients with COVID-19. Additionally, there may be differences in ACE2 expression between Asians and Occidental persons in various nephron segments, including the proximal tubules, which may explain increased risk for AKI with SARS-CoV2 in non-Asians. As more reports from other countries come out, it is becoming clearer that there are indeed regional differences in incidence of AKI, with a study from France reporting that 80% of hospitalized patients developed AKI. While there are nearly two million confirmed cases of COVID-19 in the US alone, data regarding kidney outcomes has only emerged from limited sites thus far (Table). 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 make up and health systems with different levels of resources and surge capacity. One such observational study, involving 60 sites across the US, 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 US.

While much remains to be elucidated about the novel SAR-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 1980’s the United States was hit by the AIDS epidemic. It took 2 years to identify the virus, and the first reports of HIVAN were three 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-CoV2 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 US, the next few months are a critical time to expand the investigations into COVID-19 and the kidneys. As the country sets to reopen the economy despite lack of widespread immunity, and with an effective vaccine is months away, it’s likely only a matter of months before wave 2. Thus, we will disagree with GGM 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 the 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 non-surge conditions in patients admitted with COVID-19?
2. What is the risk of AKI to chronic kidney disease (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 ATI in patients without clinical AKI, what will be the risk for CKD in COVID-19 survivors that experienced “subclinical AKI?”

4. What are the early predictors of both acute severe AKI and the predictors of non-recovery, and long-term CKD in 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-CoV2 in podocytes or through “second-hits” in patients with 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.
Disclosures

Dr. Coca is a co-founder and a member of the advisory board of RenalytixAI and owns equity in the same. In the past 3 years, he has received consulting fees from RenalytixAI, Goldfinch Bio, CHF Solutions, Quark Biopharma, Takeda Pharmaceuticals, Relypsa, Bayer, Boehringer-Ingelheim and pulse Data.

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Author Contributions

L Chan: Conceptualization; Writing - original draft; Writing - review and editing

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Table 1: Reported incidence of AKI and need for renal replacement therapy in US centers*

| Center          | Paper                        | Study Population               | n and Proportion with AKI** | Need for RRT |
|-----------------|------------------------------|--------------------------------|-----------------------------|--------------|
| Northwell Health System | Hirsch et al Kidney International\(^8\) | New York Hospitalized (N=5,449) | 1993 (37%)                  | 285 (5%)     |
| Mount Sinai Health System | Chan et al MedRXiv\(^9\) | New York Hospitalized (N=3,235) | 1406 (43%)                  | 280 (20%)    |
| Columbia        | Cummings et al Lancet\(^5\)  | New York Critically Ill (N=257) | NR                          | 79 (31%)     |
|                 | Argenziano et al MedRxiv\(^10\) | New York Hospitalized (n=1000) | 288 (33%)                   | 117 (13.8%)  |
| Oschner Health  | Mohamed et al Kidney360\(^2\) | New Orleans Hospitalized (N=575) | 161 (28%)                   | 89 (15%)     |

*Studies of 100 patients or more
**Creatinine rise ≥ 0.3 mg/dL or 50% rise from baseline
Figure 1: Proportion of reported comorbidities in studies from China and US*

*Adapted from Coca, Hiremath et al. #NephJC COVID-AKI (http://www.nephjc.com/news/covidaki)¹ and updated with US studies listed in Table 1
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