COVID-19–Associated Acute Kidney Injury
An Evolving Picture

Edward D. Siew1,2 and Bethany C. Birkelo1


Over the past 7 months, severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) has afflicted over 21 million patients and resulted in over 760,000 deaths. Rapid recognition of the extrapulmonary manifestations of infection has prompted an unprecedented rate of reports related to severe acute respiratory syndrome coronavirus 2 and AKI, mostly revealing glimpses into the varied and profound effect of infection on kidney health. However, it has also raised important questions regarding the underlying pathophysiology of kidney damage, treatment, resource management, and its public health consequences.

In this issue of CJASN, Cheng et al. (1) extend upon preliminary reports from Wuhan by providing a larger examination of the overall incidence, risk factors, and prognosis of COVID-19–associated AKI in a retrospective study of 1392 patients admitted to the Sino-French New City branch of Tongji Hospital (2). Using creatinine-based definitions, the authors found that approximately 7% of patients developed AKI, with approximately 3%, 2%, and 3% having stages 1, 2, and 3 AKI, respectively. Most were critically ill, and 15% received KRT. Approximately 95% of patients had serum D-dimer, high-sensitivity C-reactive protein, and lactate dehydrogenase levels measured, which were higher among patients with AKI than patients without AKI. Multivariable analysis demonstrated that in addition to conventional AKI risk factors, disease severity, lymphopenia, and D-dimer levels remained associated with the development of AKI. In-hospital mortality of the study cohort was 14%, although 72% of those with AKI eventually succumbed to the disease, with most also receiving mechanical ventilation and vasopressors. Among the few who survived, 19 of 28 (68%) recovered kidney function.

The authors should be commended for this contribution. The extraction and analysis of data under challenging conditions with several clinical and logistical unknowns are laudable. The extension of follow-up beyond initial preliminary reports from the first wave of COVID-19 infections also highlights that the mortality associated with AKI may be higher than these early estimates. Although the findings add important data to the existing knowledge on COVID-19–associated AKI, important knowledge gaps remain. Among these are the need to better understand the factors underpinning individual differences in the risk for AKI. The incidence of AKI in this study was one-fifth of that observed in more recent studies of hospitalized patients from Western countries (3,4). Although variation in baseline creatinine, admission thresholds, and ascertainment of kidney function may have contributed, population differences in traditional AKI risk factors were likely also important. In contrast to Western studies, including one US study in which one-half and three-quarters of patients had diabetes and hypertension (4), respectively, rates in this study were only 17% and 36%, respectively. The distribution of admission serum creatinine in the study by Cheng et al. (1) also suggested preserved kidney function, overall indicating a population at lower premorbid risk for AKI. Beyond indicating that traditional AKI risk factors are relevant for COVID-19 AKI, these findings also indicate that the public health burden of kidney disease attributable to current and future waves of infection will parallel the underlying health of the region affected. In places such as the United States, where one-third of the population is estimated to have underlying metabolic syndrome, efforts to prevent transmission will remain pivotal to reduce the toll of AKI associated with COVID-19.

These findings also highlight a critical need to better understand disease- and treatment-specific factors that drive the risk for AKI. An array of phenotypes has been identified (5), and the tracking of cases with critical illness implicates acute tubular injury as one of the predominant manifestations, a finding supported by biopsy and postmortem data. In addition to uncovering factors that drive illness severity, identifying modifiable risk factors is also imperative. One key issue intrinsic to this population surrounds the management of fluid balance. The common use of diuretics in the study by Cheng et al. (1), as well as the clustering of AKI around the time of intubation noted in others (3), highlights the tension between optimizing respiratory status and fluid resuscitation, concerns further complicated by data on myocardial dysfunction in severe disease. Although management guidelines reasonably favor more conservative fluid management, the evidence to support these recommendations remains forthcoming, and the implications are unknown. As both fluid overload and overly conservative fluid management can contribute to AKI, prospective studies are needed. Similarly, the potential contribution of...
nephrotoxic exposures has also not been well studied. Notably, more than three-fourths of patients in the study by Cheng et al. (1) also received concomitant antibiotics and antiviral agents. Although not reported, use of nonsteroidal anti-inflammatory agents (NSAI
d) may also contribute, as at least one study has demonstrated that nearly one in five hospitalized patients was prescribed NSAI
ds close to the time of admission (6). The study found a nonstatistically significant association between NSAI
d use and AKI but was limited by the use of administrative codes. Nevertheless, although clinical guidelines do not specifically recommend the avoidance of NSAI
ds, the high rates of AKI observed in some studies suggest that re-examination is warranted.

The role of more disease-specific contributions to tubular injury also remains to be examined. For example, a contribution from “sepsis-related” pathways in the pathogenesis of AKI has been hypothesized but not firmly established. Although Cheng et al. (1) observed high-sensitivity C-reactive protein levels to be elevated in most patients with AKI, definitive proof of the frequently invoked “cytokine storm” and its relative contribution to the majority of patients with AKI have been recently questioned. The infrequency of interstitial inflammation seen with the tubular injury subphenotype does not eliminate a potential contribution from systemic inflammation on local or regional hemodynamics (7). However, blood IL-6 levels in patients with COVID-19 have been observed to be lower compared with data from patients participating in previous National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Network (ARDSNet) trials (8). These findings challenge assumptions of whether the degree of inflammation in most patients is more extensive than the systemic inflammatory response seen in other infection-associated critical illness, as well as the anticipated effect of potential immunomodulatory therapies. The collection of kidney-specific data in ongoing trials testing immunomodulatory agents and more formal comparison with similarly ill non–COVID-19 populations will be essential to test this hypothesis. Another critical question that remains is whether kidney injury is caused or exacerbated by a direct cytopathic effect of the virus. Putative invasion via the angiotensin-converting enzyme-2 and Trans Membrane Serine Protease 2 has important implications for prevention, treatment, and prognosis and could partially explain why AKI rates seem to be higher with COVID-19-related illness. Whether expression is modified by angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy is also relevant to the many patients at risk for AKI who carry comorbidities necessitating treatment with these agents. Potential differences in angiotensin-converting enzyme-2 expression between races may also suggest a genetic susceptibility for tubular injury in COVID-19 infection, which could also explain some of the differences in AKI rates observed (9). However, evidence for invasion and a direct cytopathic effect on the kidney remains to be consistently demonstrated and is evolving.

Cheng et al. (1) also demonstrated that hematuria and proteinuria are common, an observation since confirmed in non-Asian populations. Although not quantified and with the baseline prevalence unknown, most proteinuria seems to be mild. The nature and type of proteinuria, its persistence, and whether it confers the same long-term prognostic significance as it does for non–COVID-19–associated AKI remain to be determined (10). Higher levels observed with AKI are consistent with the different glomerulopathies being reported; however, determining the true underlying proportion of glomerular involvement will require more prospective phenotyping.

Lastly, a clear explanation for the association between AKI and strikingly high mortality observed is lacking. Similarly high rates have been reported elsewhere (3,4), with differences partially explained by more complete follow-up in this study. Notably, Cheng et al. (1) also reported that up to 25% of patients had evidence of concomitant respiratory viral infection. The effect of the latter on this association is unclear, but it is an anticipatory concern with the coming winter. With AKI-related mortality rates seemingly higher than even observed in critically ill non–COVID-19 populations, these findings suggest that AKI in this setting may be a marker of a more ominous systemic process. For example, although its clinical relevance remains to be determined, the elevated d-dimer levels in AKI and the concomitant multiple organ failures speak to the need to better understand how endothelial function, on macro- and microvascular levels, is affected in patients with or at risk for AKI.

In summary, the last few months have informed us that the effect of COVID-19 on kidney health is significant and varied. With a staggering amount remaining to be learned, taking up this gauntlet will require leveraging the tools developed over the past 2 decades to refine our phenotyping of AKI in this disease, understand its molecular mechanisms, identify modifiable risk factors and novel treatments, and reduce the long-term implications on kidney health. The global effort mobilized to date from clinicians, investigators, and trainees has been remarkable and provides optimism that the nephrology community can meet this challenge and provide valuable insights relevant to both COVID-19–associated AKI and the AKI field as a whole.

Disclosures
E.D. Siew reports consulting for Akebia Therapeutics, Inc. in 2019; honorarium for an invited talk at the 2019 DaVita Annual Physician Leadership Conference; and royalties as an author for UpToDate. The remaining author has nothing to disclose.

Funding
E.D. Siew is supported by Health Services Research and Development award C19 20-214 and National Institute of Diabetes and Digestive and Kidney Diseases grant Vanderbilt O’Brien Kidney Center P30DK114809. B.C. Birkelo is supported by National Institute of Diabetes and Digestive and Kidney Diseases grant T32DK007569.

Acknowledgments
Because Dr. Edward D. Siew is an Associate Editor of CJASN, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript. The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendations. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility for the information and views expressed herein lies entirely with the author(s).
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Published online ahead of print. Publication date available at www.cjasn.org.