

Coronavirus Disease 2019 and Acute Kidney Injury: What Have We Learned?



Faeq Husain-Syed^{1,2}, Horst-Walter Birk¹ and Claudio Ronco^{2,3}

¹Department of Internal Medicine II, University Hospital Giessen, Justus Liebig University Giessen, Giessen, Germany; ²International Renal Research Institute of Vicenza, Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy; and ³Università di Padova, Department of Medicine (DIMED), Padua, Italy

Kidney Int Rep (2021) 6, 872–874; <https://doi.org/10.1016/j.ekir.2021.02.035>

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Kidney involvement is rapidly emerging as a prominent part of the clinical spectrum of coronavirus disease 2019 (COVID-19) and is associated with mortality.¹ Given that the angiotensin-converting enzyme 2 receptor, which is the cellular entry point for severe acute respiratory syndrome coronavirus 2, is expressed on podocytes, renal tubular epithelial cells, and endothelial cells, direct viral tissue damage is a plausible mechanism of kidney injury.² In addition, dysregulation of immune responses, microvascular thrombosis, hypovolemia, use of mechanical ventilation, hemodynamic instability, collapsing glomerulopathy, organotropism, and maladaptation of angiotensin-converting enzyme 2-related pathways have all been implicated in glomerular disease and acute tubular damage in the context of COVID-19.²

Several reports from China, Europe, and the United States suggest widely disparate rates of acute kidney injury (AKI) among hospitalized patients with COVID-19, with values ranging from 0.5% to 37.0%.² Substantial heterogeneity between geographic regions and different health systems has been reported.³ Thus, more evidence on the characteristics and outcomes of AKI from various health systems representing different populations is needed to obtain a better understanding of AKI associated with COVID-19 and to promote prevention and practical management of AKI. Due to the nature of onset of the COVID-19 pandemic, only limited data are available on the temporal change in the incidence of AKI and renal outcomes.

In this issue of *KI Reports*, Charytan *et al.*⁴ report temporal variation in AKI associated with COVID-19 at 3 university-affiliated medical centers in New York between March and August 2020. The state, which was an early epicenter of the pandemic in the United States, surpassed 30,000 deaths related to COVID-19 at the end of

August 2020.⁵ The authors analyzed data of approximately 4700 hospitalized patients with COVID-19, with 29.3% of the cohort having AKI, as diagnosed and staged according to Acute Kidney Injury Network serum creatinine (SCr) criteria. The proportion of African American participants was 14.5%. Similar to previous reports,⁶ male sex, older age, chronic kidney disease, diabetes mellitus, hypertension, congestive heart failure, and higher body mass index were independently associated with AKI. Patients with AKI were more likely to present with severe hypoxemia (oxygen saturation, <88%), have higher indices of inflammation (interleukin-6, C-reactive protein) and coagulopathy (D-dimer), be admitted to the intensive care unit, and require mechanical ventilation compared with patients with normal kidney function. AKI, older age, cancer, and congestive heart failure were independently associated with an increased risk of in-hospital death. Particularly, patients in the intensive care unit with Stage 3 AKI or those requiring renal replacement therapy (RRT) had poor outcomes, with mortality rates exceeding 75.0%.

The study has several interesting findings. First, the proportion of patients developing AKI and AKI requiring RRT decreased over time. As such, the mean rates of AKI and AKI requiring RRT in the first 2 months (March–April 2020) versus the subsequent 4 months (May–August 2020) were 32.0% (1220 cases) versus 18.0% (166 cases) and 5.9% (224 cases) versus 1.4% (13 cases), respectively. Concurrently, C-reactive protein values, age, and the proportion of patients with severe hypoxemia were markedly lower

Correspondence: Faeq Husain-Syed, University Hospital Giessen and Marburg, Department of Internal Medicine II, Division of Nephrology, Pulmonology and Critical Care Medicine, Klinikstrasse 33, 35392 Giessen, Germany. E-mail: Faeq.Husain-Syed@innere.med.uni-giessen.de

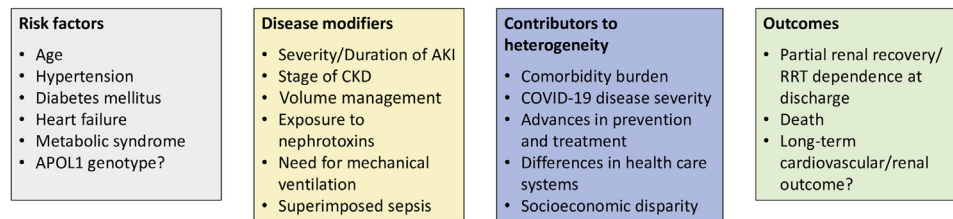


Figure 1. Acute kidney injury (AKI) associated with coronavirus disease 2019 (COVID-19). AKI associated with COVID-19 shares common risk factors and disease modifiers with AKI in other clinical settings. Several factors can contribute to the observed temporal and geographical heterogeneity in AKI rate. Although it became apparent that AKI secondary to COVID-19 is associated with an increased risk of death, more data are needed on the potential long-term consequences of AKI, including cardiovascular disease and chronic kidney disease (CKD). RRT, renal replacement therapy.

in May to August 2020. In addition, there was a trend toward a lower comorbidity burden from May to August 2020. Given the comparably low AKI rate and disease severity at admission observed in May to August 2020, it is conceivable that there may have been a shift in the distribution of AKI severity, with a higher proportion of Stage 1 AKI and a reduced proportion of Stages 2 to 3 AKI, but data to support this are not available. Second, renal recovery, defined as the absence of any SCr criteria-based stage of AKI before discharge, was observed in only 77.1% of surviving patients with AKI. Notably, the proportion of patients who demonstrated renal recovery was higher when using admission SCr or nadir SCr during hospitalization (80.4%) as opposed to outpatient SCr (70.7%) to define baseline SCr.

Many variables may contribute to the observed temporal heterogeneity in AKI in hospitalized patients with COVID-19, as described in other reports from the United States (Figure 1).³ These may include a hospital and health system overload, restrictive testing guidance limited to patients with more severe disease, and limited severe acute respiratory syndrome coronavirus 2 testing availability to estimate the real extent of the outbreak during the pandemic peak in March to April 2020. Some hospitals in New York adopted an early-intubation

strategy with limited use of high-flow nasal cannulae,⁷ and the burden of severe AKI in the setting of COVID-19 led to widespread shortages of dialysis nurses, machines, replacement fluids, and cartridges for RRT during this period. Thus, patients hospitalized in March to April 2020 were likely to be sicker, and health care system capacity constraints might have influenced patient outcomes. Notably, the ultimate decision to commence RRT is complex and still predominantly relies on clinical judgment. However, Charytan *et al.*⁴ did not report the triggers for RRT. Further information may help identify patients who are likely to benefit from RRT, as recent trials have shown that preemptive initiation of RRT in the absence of life-threatening complications of AKI may delay renal recovery and be associated with iatrogenic complications.⁸ Conversely, treatments for COVID-19 are increasingly supported by evidence,² corticosteroids are now administered early in the course of severe and critical COVID-19, and advances in the understanding of the disease course and physician familiarity in managing hospitalized patients with COVID-19 could account for the temporal shift in AKI associated with COVID-19 in the subsequent period. Other factors include the increasing proportion of younger patients with lower disease severity, in line with the report by Charytan *et al.*,⁴ and

increased emphasis on noninvasive positive pressure ventilation over intubation. In addition, differences in volume management, timing of intubation,⁶ and adherence to the Acute Respiratory Distress Network protocols for volume management may have accounted for the observed changes in the AKI rate. Regrettably, Charytan *et al.*⁴ did not provide information on the reasons for admission, and including patients with asymptomatic or pre-symptomatic severe acute respiratory syndrome coronavirus 2 infection (e.g., due to increased implementation of universal screening) may have contributed to the temporal decline in AKI rate.

COVID-19 AKI and mortality disproportionately affect the African American population, which is likely due to socioeconomic disparity,³ but the proportion of African American participants appeared to be balanced throughout the study period.

Given the multifactorial pathogenesis of AKI associated with COVID-19, patients may present with AKI or may develop AKI during the course of their hospitalization.⁶ Hypovolemia is common in early COVID-19, whereas sepsis, use of mechanical ventilation, and exposure to potentially nephrotoxic agents are important contributors to AKI during hospitalization.² Thus, it is conceivable that the report by Charytan *et al.*⁴ may have under-represented late AKI by using Acute

Kidney Injury Network criteria. These criteria give a 48-hour time-frame for diagnosing AKI, instead of the current Kidney Disease: Improving Global Outcomes consensus criteria, which consider a 7-day window for diagnosing AKI.

Finally, the high proportion of partial recovery and nonrecovery cases among AKI survivors with COVID-19 highlights the need for careful monitoring and post-AKI care to mitigate the risk of long-term adverse consequences, because AKI persistence is linked to morbidity and mortality.⁹ Similar to non-COVID-19 patients with AKI, follow-up should include serial assessment of kidney function and albuminuria and attention to blood pressure and cardiovascular risk factors. It should be noted that admission SCr or nadir SCr during hospitalization rather than outpatient SCr (or estimated SCr in patients without a reliable baseline SCr on record as recommended in the Kidney Disease: Improving Global Outcomes guideline for AKI) is likely to underestimate recovery status after AKI. This is apparent when comparing renal recovery rates after COVID-19 among different reports, which used various definitions.^{1,3} Further, any temporal variation in the proportion of AKI survivors with partial recovery and nonrecovery, if present, would need to be related to patient length of stay, as factors such as early discharge due to

limited health care system capacity may impact recovery rates. Novel tubular biomarkers may help to identify the risk of partial recovery and progression to chronic kidney disease after COVID-19, but they still remain unexplored.

In conclusion, Charytan *et al.*⁴ add to the important work accomplished in this field within the past year that has rapidly expanded our understanding of COVID-19 AKI in hospitalized patients. Future research will hopefully provide insight into AKI prevention and mitigation strategies in patients with COVID-19, as well as describe the long-term prognosis of AKI survivors.

DISCLOSURES

CR received support for acting as an advisory board member for ASAHI, Baxter, GE, Jafron, and Medtronic, and speaker's fees from Astute, bioMérieux, B. Braun, Cytosorbents, ESTOR, FMC, and Toray, all unrelated to this commentary. All the other authors declared no competing interests

AUTHOR CONTRIBUTIONS

All authors participated in drafting the manuscript and approved the final version.

ACKNOWLEDGMENTS

We thank the health care professionals on the front line of this pandemic.

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