Nephron

Clinical Practice: Second Opinion

Nephron
DOI: 10.1159/000519530

Received: July 13, 2021
Accepted: September 4, 2021
Published online: October 11, 2021

The Impact of Chronic Kidney Disease on Outcomes of Patients with COVID-19 Admitted to the Intensive Care Unit

Maureen Brogan[a] Michael J. Ross[a, b]

[a]Department of Medicine, Division of Nephrology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA; [b]Department of Development and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY, USA

Keywords
Coronavirus disease 2019 · Chronic kidney disease · ESKD · Dialysis · Intensive care unit

Abstract
Context: Coronavirus disease 2019 (COVID-19) disproportionately impacts patients with chronic kidney disease (CKD), especially those with kidney failure requiring replacement therapy (KFRT). Patients with KFRT have increased risk of developing COVID-19, and though initial reports suggested that mortality of these patients in the intensive care unit (ICU) setting is prohibitively high, those studies suffered from significant limitations. ***Subject of Review:*** The Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID) is a multicenter cohort study that enrolled adults with COVID-19 admitted to ICUs in 68 medical centers across the USA. STOP-COVID investigators compared characteristics at the time of ICU admission and clinical outcomes in 143 patients with KFRT, 521 with nondialysis-dependent CKD (ND-CKD), and 3,600 patients without CKD. Patients with KFRT were less likely to have typical COVID-19 symptoms but more likely to have altered mental status at the time of ICU admission and were less likely to require mechanical ventilation during hospitalization than those without kidney disease. Approximately, 50% of patients with KFRT and ND-CKD died within 28 days of ICU admission, and in fully adjusted models, patients with KFRT and ND-CKD had 1.41- and 1.25-fold higher risk of 28-day mortality than those without CKD. Patients with KFRT and ND-CKD were also less likely to receive emerging therapies for COVID-19 than those without CKD. ***Second Opinion:*** This study provides important new data demonstrating differences in clinical presentation in patients with KFRT and ND-CKD with COVID-19. Alhough patients with severe CKD had higher mortality than those without CKD, approximately half survived after 28 days, demonstrating that patients with COVID-19 and severe CKD can benefit from ICU care. The markedly lower use of emerging COVID-19 treatments in patients with severe CKD highlights the need to include these patients in clinical trials of new COVID-19 therapies and for clinicians to ensure equal access to care in patients with severe CKD and COVID-19.

Context

COVID-19 has caused millions of deaths worldwide since it was reported in Wuhan, China, in late 2019. Nephrologists have been at the forefront of clinical care of patients with COVID-19 as kidney-related complications,

karger@karger.com
www.karger.com/nef

Correspondence to:
Michael J. Ross, michael.ross@einsteinmed.org

Karger

including acute kidney injury (AKI), glomerular disease, and severe electrolyte derangements, are frequently encountered [1]. In addition to the deleterious effects of COVID-19 upon the kidneys, patients with chronic kidney disease (CKD) have been disproportionately impacted, especially those with kidney failure receiving chronic dialysis and kidney transplant recipients (KTR).

CKD is the most common risk factor for death in patients with COVID-19 worldwide, and the risk increases with higher CKD stage, with the highest risk occurring in those with kidney failure receiving replacement therapy (KFRT) and KTR [2–4]. Furthermore, patients with KFRT receiving in-center hemodialysis are at markedly higher risk of COVID-19 than those receiving home dialysis therapies who received care via telehealth [5]. This is likely explained by increased risk of exposure of patients receiving in-center dialysis to SARS-CoV-2 during thrice weekly travel via group or public transportation to/from dialysis and exposure to patients and staff at the dialysis unit [6–8].

Single-center studies reporting clinical outcomes in patients with CKD and COVID-19 have reported widely variable results, and this variability is due in part to differences in patient characteristics such as age, sex, race, and comorbidities that are associated with worse outcomes [4]. However, other factors, including differences in strain upon medical centers due to large numbers of patients with COVID-19, heterogeneity in data collection methods, methods used to ascertain and categorize CKD stage and clinical outcomes, and study time points, affect reported outcomes [4, 9]. Large multicenter studies that include a diverse array of medical centers across large regions and standardized and validated methods to reduce sources of variability are therefore needed.

Subject of Review

The Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID) is a multicenter cohort study involving 68 medical centers across the USA and was established in April 2020, during the peak of the COVID-19 surge in the northeastern USA. STOP-COVID enrolled consecutive adults (≥18 years) admitted to intensive care units (ICU) with laboratory-confirmed COVID-19. The overall goal of STOP-COVID is to identify independent risk factors for hospital mortality and acute organ injury and to identify treatment strategies associated with improved survival (https://clinicaltrials.gov/ct2/show/NCT04343898) [10].

In a recently published ancillary study of STOP-COVID, Flythe et al. [11] focused upon clinical outcomes in adults with pre-existing nondialysis-dependent CKD (ND-CKD) or with KFRT admitted to ICU with COVID-19 between March 4 and May 10, 2020. Patients were followed forward in historical time from ICU admission to in-hospital death, hospital discharge, or June 6, 2020, when the database was locked. There were 4,264 individuals included in the study, 143 (3%) of whom had pre-existing KFRT, 521 (12%) with ND-CKD, and 3,600 (85%) without CKD. Unsurprisingly, patients with ND-CKD and KFRT had more comorbidities, including hypertension, diabetes mellitus, and heart disease, than those without CKD. Of those with KFRT, 90% received in-center hemodialysis (HD), 6% peritoneal dialysis (PD), 1% home HD, and 3% had unknown dialysis modality.

Patients with KFRT were admitted to the ICU sooner after hospital admission (median 4 days) than patients with ND-CKD or those without CKD (7 days). Importantly, KFRT patients were less likely to have had documented COVID-19-related symptoms prior to ICU admission than those without CKD except for altered mental status, which was more common in those with KFRT (25% vs. 12%). Patients with KFRT also were less likely than those without CKD to require mechanical ventilation at the time of ICU admission (56% vs. 63%). However, patients with KFRT were more likely to require pressors at ICU admission (50%) than those with ND-CKD (42%) or without CKD (41%), though the presence of shock, defined as requirement for 2 or more pressors, was similar between groups. Baseline biomarkers also varied between groups with patients with KFRT having lower white blood counts, platelet counts, and fibrinogen levels but higher C-reactive protein (CRP), IL-6, ferritin, and troponin levels than those without CKD.

Many patients in this study received interventions intended to suppress SARS-CoV-2 and/or inflammation, despite the fact that patients in this study were enrolled before data were available from large COVID-19 clinical trials, and patients with CKD were excluded from most of those trials [12]. Most patients received hydroxychloroquine or chloroquine and fewer received azithromycin or other antiviral medications. Seven percent of patients without CKD received remdesivir compared to 2% of those with ND-CKD and 0% of those with KFRT. Although corticosteroid use was similar across groups, those without CKD were more likely to receive the IL-6 antagonist tocilizumab (19%) compared to those with ND-CKD (14%) or KFRT (9%).

In addition to being less likely to require mechanical ventilation at the time of ICU admission, patients with KFRT were less likely than those without CKD to require mechanical ventilation at any time during hospital admission (74% vs. 80%). Patients with ND-CKD or KFRT were also less likely to require prone positioning than those without CKD. Laboratory parameters differed between groups during the first 14 days of hospitalization; patients with KFRT and ND-CKD had persistently lower lymphocyte and platelet counts and higher CRP levels. Patients with KFRT had higher lactate levels during the first week of ICU care compared to other groups.

Patients with ND-CKD and KFRT had significantly higher mortality than those without CKD in unadjusted and adjusted analyses at 14 and 28 days after ICU admission. At 28 days after ICU admission, death occurred in 51% and 50% of patients with ND-CKD and KFRT but in only 35% of those without CKD. In the fully adjusted model (including age, sex, race, Hispanic ethnicity, diabetes, hypertension, coronary artery disease, heart failure, and atrial fibrillation or flutter), the hazard ratios for 28-day mortality were 1.41 and 1.25 for patients with KFRT and ND-CKD compared to those without CKD. Among those with KFRT, those dialyzing via a catheter had 1.94-fold higher risk of death than those dialyzing with an arteriovenous vascular access. Among those with ND-CKD, there was a nonsignificant trend toward higher mortality for those with baseline creatinine ≥2 mg/dL. The most common cause of death in all groups was respiratory failure. Patients with KFRT had a nonstatistically significant trend toward increased secondary outcomes, including shock, ventricular arrhythmia/cardiac arrest, and major bleeding events.

Second Opinion

Important strengths of this study include its large size, geographical diversity (though limited to the USA), standardized data collection methods, rigorous statistical analyses, and inclusion of consecutive ICU admissions, which should reduce selection bias. However, as acknowledged by the authors, there are limitations that may affect the interpretation of the results. Although patients were enrolled consecutively, data were collected retrospectively, and the study was observational. Therefore, though the investigators attempted to control for multiple factors, it remains possible that residual confounding may have affected the results. Baseline CKD status may have been misclassified in some patients, though the use of hospital laboratory data would be expected to yield more accurate assessment of kidney function than the use of diagnostic codes. Another limitation is the fact that biomarker data were missing for many patients, and it is likely that levels were checked preferentially in the more severely ill patients, which may have skewed results.

Despite the geographic diversity of study sites from all major regions of the USA, nearly all were large academic centers and 58% of patients were from the northeastern USA. Many medical centers in the northeastern USA experienced an overwhelming surge of COVID-19 during spring 2020 that necessitated a rapid expansion of ICU capacity, resulting in severely constrained nursing and other resources, including the capacity for renal replacement therapies [13–15]. STOP-COVID investigators have demonstrated that medical center strain is associated with increased mortality in critically ill patients with COVID-19 [9]. Since this study was limited to patients after ICU admission, it is also possible that patients with severe ND-CKD and/or KFRT may have experienced differences in pre-ICU care that may have affected outcomes and may have died prior to ICU admission or been denied ICU care due to perceived medical futility. However, if only "healthier" patients with severe CKD were admitted to ICU, this would have biased outcomes to be better in those with ND-CKD and KFRT.

Clinical outcomes for patients with COVID-19 have improved in the USA since the time when these data were collected, likely because health care systems have been less severely strained and due to improvements in pharmacologic and nonpharmacologic treatments [16]. It is therefore possible that patients admitted to the ICU, including those with CKD, may have better outcomes than that reported in this article. Although patients with KFRT had higher 28-day mortality than those without CKD (50% vs. 35%), mortality from single-center studies of KFRT patients with COVID-19 admitted to ICUs in the USA during the same time period was significantly higher [17–19]. The reasons for this disparity are unclear but may be explained in part by the fact that this cohort comprised mostly large academic medical centers, and measures of hospital quality and number of ICU beds are predictors of mortality in ICU patients with COVID-19 [9, 20]. It is also important to note that during the spring 2020 COVID-19 surge, there was a large increase in mortality among US patients with KFRT but a simultaneous large decrease in hospitalizations in these patients [21], strongly suggesting that a large proportion of patients with KFRT and COVID-19 died without being hospitalized.

It is unclear why patients with severe CKD were less likely to present with classic COVID-19 symptoms and more likely to present with atypical symptoms such as altered mental status, but this observation should alert clinicians to be especially vigilant for COVID-19 in patients with CKD and unexplained change in clinical status. It is also unclear why patients with KFRT were less likely to require mechanical ventilation in the ICU than patients without CKD. Since patients with KFRT had a higher prevalence of vasopressor use at the time of ICU admission, clinicians may have admitted them to the ICU over concerns of worsening hemodynamics during renal replacement therapy.

The reasons why CKD is an independent risk factor for death in patients with COVID-19 are poorly understood. The most common causes of death in STOP-COVID were respiratory failure, septic shock, and kidney failure [10]. The presence of severe kidney disease can make assessment and optimization of volume status in patients with respiratory failure more difficult. Also, since CKD is a potent risk factor for AKI in patients with COVID-19 [13] and AKI is strongly associated with increased mortality in patients with COVID-19 [13, 15], increased AKI may have contributed to excess mortality in ND-CKD. Moreover, persons with ND-CKD and KFRT are also at increased risk of bacterial infections and poor outcomes after infection than those without CKD [22]. Although patients with CKD did not have markedly increased prevalence of bacteremia at the time of ICU admission in STOP-COVID, it is unclear whether there were more episodes of bacteremia during the subsequent ICU course in patients with CKD. This is particularly relevant for patients with KFRT since HD catheter use compared to arteriovenous access was associated with nearly 2-fold increased mortality in this study.

Although the increased mortality attributable to CKD in patients with COVID-19 likely reflects differences in underlying physiology, including dysregulated immune responses, since these patients were less likely to receive immunomodulatory and antiviral therapies, it is also possible that differences in clinical care may have contributed to worsened outcomes. One of the most important results from this study was the lower incidence of treatment with emerging therapies that clinicians thought might improve outcomes in COVID-19. Although some, such as remdesivir, are not recommended for patients with eGFR <30 mL/min/1.73 m^2, others, such as tocilizumab, are not contraindicated and do not require dose adjustment for reduced GFR. Although the limited efficacy of these treatments would not fully explain the marked difference in mortality in patients with CKD, there may have been other unmeasured differences in care between those with/without CKD that may have influenced mortality. Unfortunately, patients with kidney disease are often denied potentially beneficial medical therapies due to inappropriate concerns over safety or futility [23, 24]. This "renalism" may adversely impact the care of patients with COVID-19 and kidney disease, and clinicians should be vigilant to ensure kidney patients are not denied potentially beneficial treatments and that patients with kidney disease are well represented in clinical trials for COVID-19 therapies. Although the results of this study demonstrating higher mortality of patients with COVID-19 and severe CKD may be helpful in informing clinicians and patients and family members when discussing goals of care, it is important that severe CKD not be used to justify therapeutic nihilism in this vulnerable population.

In conclusion, the study by Flythe et al. [11] provides important insights regarding clinical outcomes in critically ill patients with CKD and COVID-19. Although mortality was higher in those with CKD than those without CKD, approximately 50% survived during a period when COVID-19 mortality was especially high in the USA. This demonstrates that patients with CKD, including those with KFRT, can benefit from ICU care. Importantly, this study also demonstrates that patients with CKD were far less likely to receive immunomodulatory and anti-SARS-CoV-2 therapies, thereby highlighting the urgent need for inclusion of patients with CKD, including those with KFRT, in COVID-19 clinical trials.

Conflict of Interest Statement

Dr. Brogan has no disclosures. Dr. Ross has served as a consultant to Aria Pharmaceuticals and Catalys Pacific, LLC. He has also received honoraria from the American College of Physicians and Ebix/Oakstone Publishing.

Funding Sources

M.J. Ross was funded by NIH/NIDDK grants R01DK101338 and R01DK108346.

Author Contributions

Drs. Brogan and Ross co-wrote the entirety of the manuscript.

References

1 Bruchfeld A. The COVID-19 pandemic: consequences for nephrology. Nat Rev Nephrol. 2021 Feb;17(2):81–2.
2 Gansevoort RT, Hilbrands LB. CKD is a key risk factor for COVID-19 mortality. Nat Rev Nephrol. 2020 Dec;16(12):705–6.
3 Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using openSAFELY. Nature. 2020 Aug;584(7821):430–6.
4 Council E-E, Ortiz A, Cozzolino M, Fliser D, Fouque D, Goumenos D, et al. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. Nephrol Dial Transplant. 2021 Jan 1;36(1):87–94.
5 Lew SQ, Wallace EL, Srivatana V, Warady BA, Watnick S, Hood J, et al. Telehealth for home dialysis in COVID-19 and beyond: a perspective from the American Society of Nephrology COVID-19 home dialysis subcommittee. Am J Kidney Dis. 2021 Jan;77(1):142–8.
6 Corbett RW, Blakey S, Nitsch D, Loucaidou M, McLean A, Duncan N, et al. Epidemiology of COVID-19 in an urban dialysis center. J Am Soc Nephrol. 2020 Aug;31(8):1815–23.
7 Hsu CM, Weiner DE, Aweh G, Salenger P, Johnson DS, Lacson E Jr. Epidemiology and outcomes of COVID-19 in home dialysis patients compared with in-center dialysis patients. J Am Soc Nephrol. 2021 Jun 9; ASN.2020111653. Epub ahead of print.
8 Perl J, Thomas D, Tang Y, Yeung A, Ip J, Oliver MJ, et al. COVID-19 among adults receiving home versus in-center dialysis. Clin J Am Soc Nephrol. 2021 Sep;16(9):1410–2.
9 Churpek MM, Gupta S, Spicer AB, Parker WF, Fahrenbach J, Brenner SK, et al. Hospital-level variation in death for critically ill patients with COVID-19. Am J Respir Crit Care Med. 2021 Apr 23. Epub ahead of print.
10 Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med. 2020 Nov 1;180(11):1436–47.
11 Flythe JE, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J, et al. Characteristics and outcomes of individuals with pre-existing kidney disease and COVID-19 admitted to intensive care units in the United States. Am J Kidney Dis. 2021 Feb;77(2):190–203.e1.
12 Major R, Selvaskandan H, Makkeyah YM, Hull K, Kuverji A, Graham-Brown M. The exclusion of patients with CKD in prospectively registered interventional trials for COVID-19-a rapid review of international registry data. J Am Soc Nephrol. 2020 Oct;31(10):2250–2.
13 Fisher M, Neugarten J, Bellin E, Yunes M, Stahl L, Johns TS, et al. AKI in hospitalized patients with and without COVID-19: a Comparison Study. J Am Soc Nephrol. 2020 Sep;31(9):2145–57.
14 Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020 Jul;98(1):209–18.
15 Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol. 2021 Jan;32(1):151–60.
16 Lee CK, Linder JA, Gates KL. Management of severe covid-19: progress and promise. BMJ. 2021 May 7;373:n1147.
17 Fisher M, Yunes M, Mokrzycki MH, Golestaneh L, Alahiri E, Coco M. Chronic hemodialysis patients hospitalized with COVID-19: short-term outcomes in the Bronx, New York. Kidney360. 2020;1(8):755–62.
18 Ma Y, Diao B, Lv X, Zhu J, Chen C, Liu L, et al. Epidemiological, clinical, and immunological features of a cluster of COVID-19-contracted hemodialysis patients. Kidney Int Rep. 2020 Aug;5(8):1333–41.
19 Valeri AM, Robbins-Juarez SY, Stevens JS, Ahn W, Rao MK, Radhakrishnan J, et al. Presentation and outcomes of patients with ESKD and COVID-19. J Am Soc Nephrol. 2020 Jul;31(7):1409–15.
20 Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. J Am Soc Nephrol. 2021 Jan;32(1):161–76.
21 System USRD. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD.
22 Naqvi SB, Collins AJ. Infectious complications in chronic kidney disease. Adv Chronic Kidney Dis. 2006 Jul;13(3):199–204.
23 Chertow GM, Normand SL, McNeil BJ. "Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. J Am Soc Nephrol. 2004 Sep;15(9):2462–8.
24 Weisbord SD. AKI and medical care after coronary angiography: renalism revisited. Clin J Am Soc Nephrol. 2014 Nov 7;9(11):1823–5.