

COVID-19 Among Hospitalized Patients with Kidney Disease: Experience at a US Midwestern Academic Medical Center

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ABSTRACT

Objective: We sought to characterize the clinical profiles and outcomes of patients with coronavirus disease 2019 and comorbid kidney disease hospitalized at a U.S. urban, Midwestern tertiary care hospital.

Methods: In this single-center observational study, we describe 205 patients with acute kidney injury (n = 98), dialysis-dependent chronic kidney disease stage 5 (n = 54), or kidney transplant (n = 53), admitted during the first surge of the local pandemic, from March 19, 2020, to July 31, 2021.

Results: Most patients in the cohort were African American (acute kidney injury, 51%; dialysis-dependent chronic kidney disease stage 5, 82%; kidney transplant, 62%), and obesity was common (acute kidney injury, 53%; dialysis-dependent chronic kidney disease stage 5, 44%; kidney transplant, 59%). Mechanical ventilation was required in 50% of the acute kidney injury, 22% of the dialysis-dependent chronic kidney disease stage 5, and 13% of the kidney transplant recipients. Nearly half of the acute kidney injury patients (46%) died and 49% required kidney replacement therapy, while in-hospital mortality was 24% in the dialysis-dependent chronic kidney disease stage 5 patients and 9% in the kidney transplant recipients. Logistic regression analysis identified older age and patient group as leading correlates of mortality, with lower death risk in kidney transplant (24%; odds ratio (OR), 0.17; 95% CI 0.06-0.47) and dialysis-dependent chronic kidney disease stage 5 (9%; OR, 0.36; 95% CI 0.16-0.78) patients compared to acute kidney injury patients (46%). Obesity was associated with a 5-fold increased mortality risk in the coronavirus disease 2019 patients with acute kidney injury (OR, 5.32; 95% CI 1.41-20.03) but not in dialysis-dependent chronic kidney disease stage 5 or kidney transplant patients.

Conclusions: During the first surge of the pandemic, kidney patients hospitalized with coronavirus disease 2019 experienced high mortality, especially those with acute kidney injury, older age, and obesity. Identifying those at the highest risk for adverse outcomes may direct preventative strategies including counseling on vaccination.

Keywords: Acute kidney injury, coronavirus disease-2019, COVID-19, dialysis, mortality, obesity, outcomes, transplant

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has profoundly impacted communities across the world. However, certain subgroups including patients with chronic kidney disease (CKD) and kidney transplant (KTx) recipients are particularly vulnerable to adverse outcomes of COVID-19.¹⁻⁷ Coronavirus disease-2019 incidence and outcomes within the general population, as well as

patients with kidney diseases, have varied by geography, age, race, and ethnicity.^{3,8} The pandemic has disproportionately affected certain populations including racial and ethnic minorities and patients with some comorbidities and social risk factors.⁸⁻¹⁰ As nephrology providers caring for kidney patients at a U.S. urban, Midwestern tertiary care hospital, we sought to characterize the clinical profiles and outcomes of patients with COVID-19 and co-morbid kidney disease hospitalized at our center.



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METHODS

Data Source and Study Population

In this single-center observational study, we examined the characteristics, presentations, treatment, and in-hospital outcomes of patients with kidney diseases admitted to Saint Louis University Hospital with COVID-19 during the first surge of the local pandemic, from March 19, 2020, to July 31, 2021. Included patients were aged 18 years or older, found to have COVID-19, and hospitalized at Saint Louis University Hospital during the observation period. The electronic health record (EHR) was reviewed for information on patient demographic and clinical characteristics (age, sex, ethnicity, primary kidney disease, body mass index (BMI), comorbid conditions, kidney replacement therapy (KRT) modalities, date of KTx, and donor type), laboratory findings, medications, and outcomes. Diagnosis of COVID-19 was ascertained by a positive result on polymerase chain reaction assay of nasal and/or pharyngeal swab specimens performed in our health system or by a COVID-19 indicator in the EHR.

Patients were categorized into acute kidney injury (AKI), dialysis-dependent CKD stage 5 (CKD-5D), or KTx groups. Acute kidney injury was defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria of increase in serum creatinine by 0.3 mg/dL or more within 48 hours or an increase in serum creatinine at least 1.5-times baseline within the last 7 days.¹¹ The study was approved by the Saint Louis University University Institutional Review Board (protocol number 31323). Given the retrospective and low-risk nature of the study, approval included a waiver of individual informed consent.

MAIN POINTS

- In this single-center cohort of patients with coronavirus disease 2019 (COVID-19) and kidney disease hospitalized in the first surge of our local pandemic, we observed high rates of respiratory failure, kidney replacement therapy needs, and mortality, especially in those with acute kidney injury (AKI).
- Mortality was the highest in older patients and in obese patients with AKI.
- While all kidney patients should be counseled on adherence to COVID-19 prevention measures including vaccination, understanding risk factors for morbidity and mortality associated with COVID-19 in this cohort targets reinforcement to especially vulnerable sub-groups.
- In our local experience, sharing these data in routine counseling has motivated some patients with vaccine hesitancy to pursue vaccination.
- Considerations in new surges include the benefits of additional vaccine doses, use of monoclonal antibodies for early disease or preexposure prophylaxis, oral antiviral treatments, and for transplant candidates, emerging use of organs from donors with a history of COVID-19 for transplantation.
- Continued study and monitoring are needed to optimize the care of these vulnerable patients through ongoing surges of the pandemic.

Table 1. Demographic and Comorbidity Profiles of the Study Cohort

	AKI (N = 98)	CKD-5D (N = 54)	Transplant (N = 53)
Age, mean ± SD	63.3 ± 14.2	62.6 ± 13.9	54.1 ± 13.0†
Sex: n (%)			
Male	62 (63.3)	30 (55.6)	31 (58.5)
Female	36 (36.7)	24 (44.4)	22 (41.5)
BMI (kg/m ²), mean ± SD	32.0 ± 9.6	29.1 ± 7.1	31.9 ± 6.4
<18.5 kg/m ² , n (%)	4 (4.08)	4 (7.41)	0
18.5 to < 25 kg/m ² , n (%)	17 (17.4)	14 (25.9)	8 (15.1)
25 to <30 kg/m ² , n (%)	25 (25.5)	12 (22.2)	14 (26.4)
≥30 kg/m ² , n (%)	52 (53.1)	24 (44.4)	31 (58.5)
Race, n (%)			
Black	50 (51.0)	44 (81.5)	33 (62.3)
White	43 (43.9)	5 (9.3)	18 (34.0)
Other	5 (5.1)	5 (9.3)	2 (3.8)
Ethnicity, n (%)			
Hispanic	4 (4.1)	1 (1.9)	1 (1.9)
Non-Hispanic	94 (95.9)	53 (98.1)	52 (98.1)
Cause of kidney disease, n (%)			
Diabetic nephropathy	24 (24.5)	33 (61.1)	18 (34.0)
Hypertension	25 (25.5)	16 (29.6)	19 (35.9)
Glomerulonephritis	0	2 (3.7)	5 (9.4)
Other	49 (50.0)	3 (5.6)	11 (20.7)
Comorbidities, n (%)			
Chronic kidney disease	30 (30.6)	54 (100%)	53 (100%)
Coronary artery disease	15 (15.3)	15 (27.8)	7 (13.2)
Hypertension	78 (79.6)	52 (96.3)*	50 (94.3)*
Diabetes	45 (45.9)	34 (63.0)*	25 (47.2)
Congestive heart disease	23 (23.5)	24 (44.4)*	5 (9.4)*
Underlying lung disease	24 (24.5)	13 (24.1)	10 (18.9)
Malignancy	11 (11.2)	1 (1.9)	0
Cirrhosis	9 (9.2)	0	1 (1.9)
Tobacco use, n (%)			
Current	13 (13.3)	7 (13.0)	0
Prior	36 (36.7)	19 (35.2)	21 (39.6)
Never/unknown	49 (50.0)	28 (51.8)	32 (60.4)

% reflects distributions of characteristics within the kidney groups.

P values: *P ≤ 0.001-0.05; †.0001 ≤ P < .001; ‡P < .0001 for differences in trait distributions compared to AKI group.

AKI, acute kidney injury; BMI, body mass index; CKD-5D, chronic kidney disease stage 5 on dialysis; SD, standard deviation.

Outcomes

The primary study outcome was in-hospital mortality and secondary outcomes included mechanical ventilation requirements, KRT requirements, hospital length of stay, and intensive care unit admissions and length of stay. Observation extended from the date of hospitalization to the date of hospital discharge or death.

Statistical Analyses

Data management and analyses were performed with SAS for Windows software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical data were presented as counts and proportions and compared between groups (e.g., patient with different kidney replacement modalities) using the chi-square test. Continuous data were presented as means and ranges and

compared using analysis of variance. The Kruskal–Wallis with post hoc analyses was performed for non-normally distributed data. Logistic regression was used to assess the adjusted odds ratio (OR) of mortality [OR, 95% CI] in the presence of multiple variables. $P < .05$ was considered significantly significant.

RESULTS

Cohort and Characteristics

We identified 205 patients with AKI ($n = 98$), CKD-5D ($n = 54$), or KTx ($n = 53$) admitted during the first surge of the local pandemic (Table 1). Monthly hospitalized cases of COVID-19 in kidney patients at our center ranged from 6 at the start of the pandemic to a peak of 35 cases in December 2020 and then began to decline at the end of the first surge (Figure 1A).

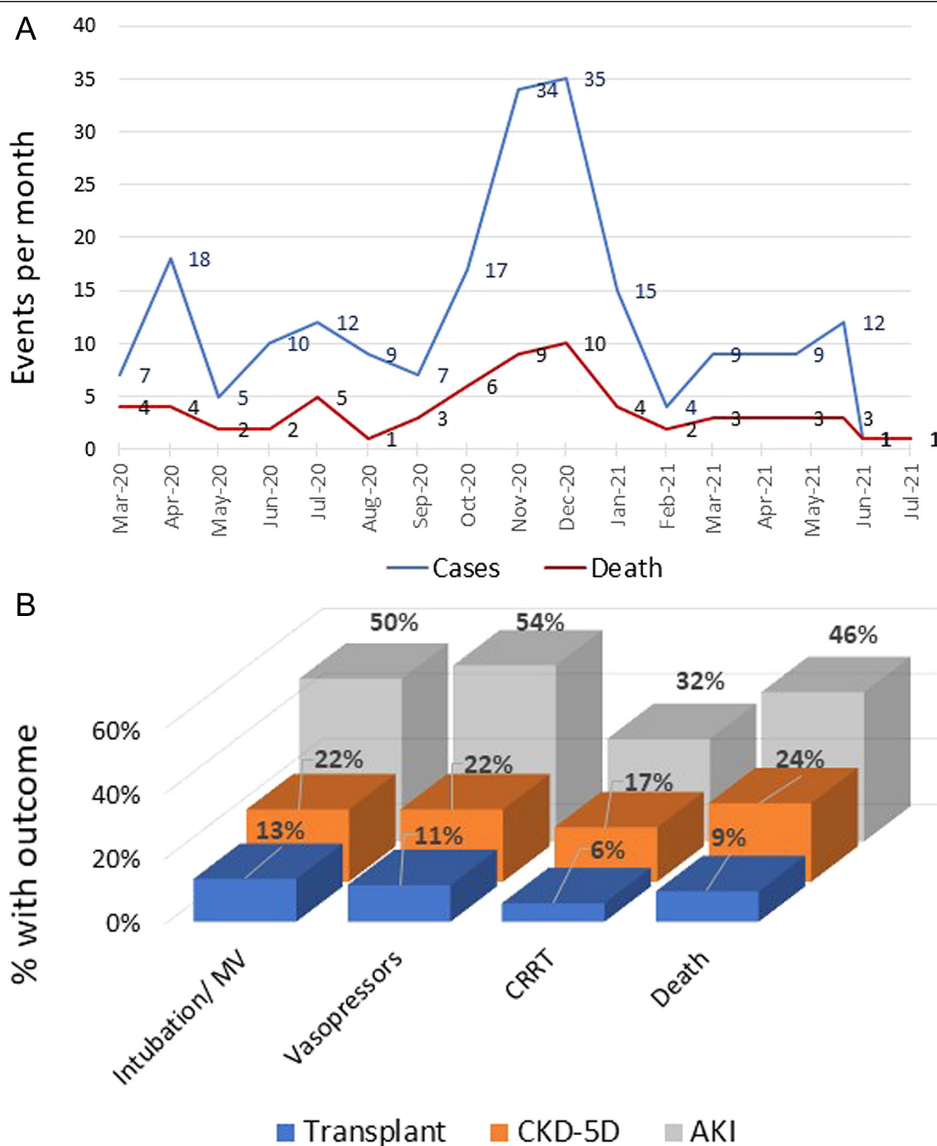


Figure 1. (A) Monthly rates of hospitalized kidney patients with COVID-19 and in-hospital mortality. (B) Clinical outcomes of hospitalized kidney patients with COVID-19. AKI, acute kidney injury; CKD-5D, chronic kidney disease stage 5 on chronic dialysis; CRRT, continuous renal replacement therapy; MV, mechanical ventilation.

Table 2. Presenting Clinical Characteristics and Treatments in the Cohort

	AKI (N = 98)	CKD-5D (N = 54)	Transplant (N = 53)
Baseline serum creatinine (mg/dL), mean \pm SD	1.6 \pm 1.2	6.2 \pm 3.0*	1.9 \pm 1.4
Presenting symptoms, n (%)			
Fever	32 (32.7)	22 (40.7)	22 (41.5)
Shortness of breath	66 (67.4)	25 (46.3)*	20 (37.7)*
Cough	37 (37.8)	16 (29.6)	26 (49.1)
Other	44 (44.9)	23 (42.6)	24 (45.3)
ACE inhibitor/ARB use at presentation, n (%)	1 (1.0)	14 (25.9)	15 (28.3)
KTx immunosuppression, n (%)			
Steroids	–	–	48 (90.6)
CNIs (tacrolimus/cyclosporine A)	–	–	51 (96.2)
MPA derivative (mycophenolate mofetil/ sodium)	–	–	28 (52.8)
Treatment for COVID-19, n (%)			
Hydroxychloroquine	4 (4.1)	6 (11.1)	2 (3.8)
Azithromycin	29 (29.6)	9 (16.7)	7 (13.2)*
Convalescent serum or plasma	9 (9.2)	0	2 (3.8)
Remdesivir	20 (20.4)	2 (3.7)*	7 (13.2)
Dexamethasone	57 (58.2)	22 (40.7)*	20 (37.7)*
Tocilizumab	3 (3.1)	0	1 (1.9)

% reflects distributions of characteristics within the kidney groups.
P values: * $P \leq .001$ -.05; †.0001 $\leq P < .001$; ‡ $P < .000$ for differences in trait distributions compared to AKI group.
ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CKD-5D, chronic kidney disease stage 5 on chronic dialysis; CNI, calcineurin inhibitor; MPA, mycophenolic acid; SD, standard deviation.

The mean age in the AKI, CKD-5D, and KTx groups was 63.3 \pm 14.2, 62.6 \pm 13.9, and 54.1 \pm 13.0 years, respectively. Women comprised 37% of AKI cases, 44% of CKD-5D cases, and 42% of the affected KTx recipients. The majority of patients (62%) were African American (51% in AKI, 82% in CKD-5D, and 62% in KTx groups). Mean BMI was 32.0 \pm 9, 29.1 \pm 7.1, and 31.9 \pm 6.4 kg/m², and obesity (BMI >30 kg/m²) was present in 53%, 44%, and 59% of the AKI, CKD-5D, and KTx groups, respectively.

All kidney patients in the cohort had at least 1 additional comorbidity, including hypertension (79%), diabetes (51%), congestive heart failure (25%), underlying lung disease (23%),

or coronary artery disease (18%). Among the patients with AKI, 31% had underlying CKD, predominantly due to diabetic nephropathy and hypertension, and diabetic nephropathy was also the most common cause of kidney failure (61%) in patients with CKD-5D.

Clinical Presentations and Treatments

The most common presenting symptoms included shortness of breath in 67% of AKI and 46% of CKD-5D patients and cough in 49% of KTx recipients (Table 2). Among the kidney transplant recipients, immunosuppression at presentation included steroids in 91%, calcineurin inhibitors in 96%, and mycophenolic acid (MPA) in 53%. The most common medical COVID-19 treatment was dexamethasone, administered to 58% of those with AKI, 41% with CKD-5D, and 38% of KTx patients. Remdesivir was used in 20%, 4%, and 13% of the AKI, CKD-5D, and KTx patients, respectively.

Outcomes

Mean length of hospital stay was 20+15, 13+15, and 8+13 days in the AKI, CKD-5D, and KTx patients, including intensive care requirements in 67%, 28%, and 17%, respectively. Approximately half of the AKI patients (53%) required RRT and 8% were treated with extracorporeal membrane oxygenation (Table 3). Twelve percent of KTx recipients received intermittent or continuous dialysis. Mechanical ventilation was required in 50% of the AKI, 22% of the CKD-5D, and 13% of the KTx recipients (Figure 1B). Nearly half of the AKI group (46%) died, while in-hospital mortality was 24% in the CKD-5D patients and 9% in the KTx recipients (Table 3). Logistic regression analysis identified older age (OR per decade, 1.57; 95% CI 1.18-2.07; $P = .002$) and patient group as significant correlates of mortality in hospitalized kidney patients with COVID-19 mortality, with lower death risk in the KTx (OR, 0.17; 95% CI 0.06-0.47; $P = .0007$) and CKD-5D (OR, 0.36; 95% CI 0.16-0.78; $P = .01$) compared to AKI patients. Obesity defined as BMI >30 kg/m² (vs. BMI 18.5 to <25) was associated with increased mortality risk in the COVID-19 patients with AKI (OR, 5.32; 95% CI 1.41-20.03; $P = .01$) but not in CKD-5D (OR, 0.40; 95% CI 0.08-2.11) or KTx patients (OR, 1.21; 95% CI 0.10-14.09).

DISCUSSION

In this single-center cohort of patients with COVID-19 and kidney disease hospitalized in the first surge of our local pandemic, we observed high rates of respiratory failure, RRT needs, and mortality, especially in those with AKI. Older age and patient group were independent correlates of mortality, which was lower in the CKD-5D and KTx compared to AKI patients in our cohort. Obesity was associated with 5-times the mortality as normal BMI in the COVID-19 patients with AKI (OR, 5.15; 95% CI 1.38-19.22) but not in CKD-5D or KTx patients.

Previous studies have reported high mortality among COVID-19 patients with AKI.¹²⁻¹⁴ Studies of KTx recipients hospitalized with COVID-19 have also estimated high mortality in the

Table 3. Clinical Course and Outcomes of the Study Cohort

	AKI (N = 98)	CKD-5D (N = 54)	Transplant (N = 53)
Duration of hospital stay (day), mean \pm SD	19.7 \pm 15.4	12.7 \pm 14.9*	8.1 \pm 13.1*
ICU admission, n (%)	66 (67.4)	15 (27.8)*	9 (17.0)*
Duration of ICU stay (days): mean \pm SD	17.8 \pm 15.8	13.7 \pm 21.9*	7.3 \pm 9.4*
COVID-19 complications, n (%)			
Acute liver injury	16 (16.3)	6 (11.1)	0*
Cardiomyopathy	18 (18.4)	4 (7.4)	0*
Rhabdomyolysis	2 (2.0)	0	0
Respiratory support, n (%)			
Nasal cannula or simple face mask	21 (21.4)	23 (42.6)*	9 (17.0)
High-flow nasal cannula	15 (15.3)	2 (3.7)*	5 (9.4)
Non-invasive (CPAP or BIPAP)	12 (12.4)	1 (1.9)	4 (7.6)
Intubation/mechanical ventilation	49 (50.0)	12 (22.2)*	7 (13.2)*
ECMO	8 (8.2)	0	0
Other	8 (8.2)	0	0
Circulatory support, n (%)			
Vasopressors	53 (54.1)	12 (22.2)*	6 (11.3)*
Inotropes	23 (23.5)	1 (1.9)*	0*
Mechanical circulatory support	4 (4.1)	0	0
RRT requirement, n (%)			
New intermittent HD	21 (21.4)	–	3 (5.7)*
CRRT	31 (31.6)	9 (16.7)*	3 (5.7)*
Mortality, n (%)	45 (45.9)	13 (24.1)*	5 (9.4)*
Cause of death, n (%)			
Acute respiratory distress syndrome	17 (37.8)	1 (7.7)	1 (20.0)
Hypoxia/AHRF	13 (28.9)	5 (38.5)	3 (60.0)
Sepsis	6 (13.3)	1 (7.7)	0
Other	9 (20.0)	6 (46.1)	1 (20.0)

% reflects distributions of characteristics within the kidney groups.

P values: * $P \leq .001$ -.05; † $0.001 \leq P < .001$; ‡ $P < .000$ for differences in trait distributions compared to AKI group.

AHRF, acute hypoxic respiratory failure; AKI, acute kidney injury; BIPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; ICU, intensive care unit; RAS, renin angiotensin system; KRT, kidney replacement therapy; SD, standard deviation.

range of 20%-40%, compared with 10%-15% mortality among general hospitalized patients with COVID-19.⁹ Other studies found higher mortality rates in hospitalized COVID-19 patients with CKD and chronic hemodialysis dependence when compared with KTx patients.^{15,16} In these studies, the worst outcome were seen in CKD patients presenting with AKI on CKD.^{15,16} The somewhat lower mortality rate in our hospitalized KTx recipients compared to previous reports may be related to different admission criteria and/or other factors including recipient age, donor source, induction, and maintenance immunosuppression, as well as variation given the sample size. Increased mortality risk from COVID-19 in previous KTx cohorts has been reported with older age, other medical comorbidities, and receipt of deceased donor allografts but not with obesity.⁹ In our cohort, the mean age of the KTx group was 54 years. In a recent meta-analysis of KTx recipients with COVID-19, survivors were younger than non-survivors (mean age 54.9 versus 67.5 years, respectively). Similar to the present study, obesity prevalence did not differ in the surviving (46.8%) versus non-surviving (49.8%) KTx recipients. Immunosuppressive treatment, especially MPA, was initially suggested to impact COVID-19 outcomes.¹⁷ Currently, the general approach at many transplant centers is to moderately decrease the overall amount of immunosuppression with a particular emphasis on decreasing or stopping antimetabolite drugs such as MPA or azathioprine. This approach is based on expert opinion developed in conjunction with various professional societies.¹⁷ Among the 5 KTx patients who died in our cohort, 2 (40%) were taking MPA at admission, while 54% of survivors were taking triple immunosuppressive treatment including MPA. The potential impacts of immunosuppressive treatment on outcomes require further investigation and will evolve as SARS-CoV-2 antivirals with strong drug-drug interactions with calcineurin inhibitors (nirmatrelvir/ritonavir) become available. Case fatality may also be impacted by access to care and disease severity at presentation. It is possible that transplant patients were hospitalized with milder illness at our hospital during the first COVID-19 surge, contributing to lower observed mortality.

Obesity has been identified as a risk factor for COVID-19 mortality in the general population.^{14,18} Similarly, obesity is also found to be a strong correlate of 5-fold increased mortality in COVID-19 patients with AKI hospitalized at our center. However, this association was not observed among CKD-5D or KTx groups in our cohort. Obesity and mortality have a paradoxical relationship in the dialysis population, with obesity associated with a survival advantage, particularly in those receiving hemodialysis.¹⁹ Potential causes of the obesity paradox in CKD-5D patients may include a more stable hemodynamic status, alterations in circulating cytokines, less malnutrition-associated inflammation, and distinctive neurohormonal patterns. While obesity was not significantly associated with lower mortality in CKD-5D patients with COVID-19, the odds ratio point estimate was less than 1.0. While more work is needed to understand the interplay of inflammation, obesity, and kidney disease in

COVID-19-related outcomes, in our population, we consider obesity as a risk factor to reinforce counseling on the importance of COVID-19 prevention strategies, especially in the pre-dialysis CKD population at risk for AKI with COVID-19.

To date, several other risk factors have been described for adverse outcomes including mortality in kidney patients with COVID-19, including older age, male sex, Black race, diabetes, and cardiac disease.²⁰⁻²³ Our study corroborates the role of older age as a risk factor for death in kidney patients with COVID-19, and as with obese patients, we counsel older kidney patients on the need for vigilance in preventative measures against COVID-19. We did not observe racial variation in outcomes, but this pattern may be impacted by the predominantly Black racial composition of our cohort. Our relatively small sample size limited statistical power for the detection of other risk relationships but also emphasizes the importance of observed relationships with age and with obesity in the AKI group. Another limitation of the study is that AKI stages were not specified.

Treatments for COVID-19 have evolved over the pandemic. In the first surge, early use of hydroxychloroquine and azithromycin was replaced by dexamethasone and remdesivir as evidence evolved. Although there is a concern for accumulation of the carrier sulfobutylether- β -cyclodextrin of remdesivir in patients with low estimated glomerular filtration rate (eGFR), emerging studies suggest, the safety of remdesivir use in renally impaired COVID-19 patients with eGFR < 30 mL/min and the potential benefit outweighing the theoretical risk of liver or kidney toxicity.^{24,25} However, remdesivir use was lower in our cohort, especially in CKD-5D and KTx pat. Although further clinical trials are needed to improve knowledge on the safety and efficacy of remdesivir, well conducted retrospective studies can also inform and help providers with clinical decision-making on remdesivir use in patients with kidney diseases.

Given the rapidly changing landscape of COVID-19 incidence, vaccination, and treatment approaches, understanding the key drivers of COVID-19 outcomes in kidney patient cohorts is challenging. Vaccinations became available to high-risk patients in late 2020, and availability grew with increased supplies. Notably, emerging data demonstrated decreased antibody responses to vaccination among immunosuppressed patients such as transplant recipients, warranting vaccine boosters. Further, despite the high risks of COVID-19, vaccine hesitancy persists in some groups.²⁶ While discerning the impacts of rapidly changing practices is challenging, tracking cohorts can be useful for understanding resource utilization, comparing outcomes across centers and geography, and looking for factors that may predict better or worse outcomes.

In summary, we observed high rates of COVID-19-related respiratory failure, RRT needs, and mortality in patients with kidney disease hospitalized in the first surge of our local pandemic,

especially in those with AKI. Mortality was highest in older patients and in obese patients with AKI. While all kidney patients should be counseled on the adherence to COVID-19 prevention measures including vaccination, understanding the risk factors for morbidity and mortality associated with COVID-19 in this cohort directs reinforcement to especially vulnerable subgroups. In our local experience, sharing these data in routine counseling has motivated some patients with vaccine hesitancy to pursue vaccination. Considerations in new surges include the benefits of additional vaccine doses, use of monoclonal antibodies for early disease or preexposure prophylaxis, oral antiviral treatments, and for transplant candidates, emerging use of organs from donors with a history of COVID-19 for transplantation.²⁷ Continued study and monitoring are needed as we seek to optimize the care of these vulnerable patients through ongoing surges of the pandemic.

Ethics Committee Approval: The survey was approved by the Saint Louis University Institutional Review Board (Date: June 09, 2020, Decision number: 31323).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.C., K.L.L.; Design – Y.C., S.P., KLL; Supervision – YC, KLL; Funding – KLL; Data Collection– YC, SP, AS, AAM, FAR, UE; Analysis and/or Interpretation – YC, SP, KLL; Literature Review – YC, SP, AAM, KLL; Writing – YC, KLL; Critical Review – YC, SP, AS, AAM, FAR, UE, MP, KM, TV, AM, TG, JCE, KLL

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Declaration of Interests: The authors declare that they have no competing interest.

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