Kidney360

A Comparison Study of Coronavirus Disease 2019 Outcomes in Hospitalized Kidney Transplant Recipients

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect any human host, but kidney transplant recipients (KTR) are considered more susceptible on the basis of previous experience with other viral infections. We evaluated rates of hospital complications between SARS-CoV-2–positive KTR and comparator groups.

Methods We extracted data from the electronic health record on patients who were hospitalized with SARS-CoV-2, testing at six hospitals from March 4 through September 9, 2020. We compared outcomes between SARS-CoV-2–positive KTR and controls: SARS-CoV-2–positive non-KTR, SARS-CoV-2–negative KTR, and SARS-CoV-2–negative non-KTR.

Results Of 31,540 inpatients, 3213 tested positive for SARS-CoV-2. There were 32 SARS-CoV-2–positive and 224 SARS-CoV-2–negative KTR. SARS-CoV-2–positive KTR had higher ferritin levels (1412; interquartile range, 748–1749 versus 553; interquartile range, 256–1035; $P<0.01$) compared with SARS-CoV-2–positive non-KTR. SARS-CoV-2–positive KTR had higher rates of ventilation (34% versus 14%, $P<0.01$; versus 9%, $P<0.01$; versus 5%, $P<0.01$), vasopressor use (41% versus 16%, $P<0.01$; versus 17%, $P<0.01$; versus 12%, $P<0.01$), and AKI (47% versus 15%, $P<0.01$; versus 23%, $P<0.01$; versus 10%, $P<0.01$) compared with SARS-CoV-2–positive non-KTR, SARS-CoV-2–negative KTR, and SARS-CoV-2–negative non-KTR, respectively. SARS-CoV-2–positive KTR continued to have increased odds of ventilation, vasopressor use, and AKI compared with SARS-CoV-2–positive non-KTR independent of Elixhauser score, Black race, and baseline eGFR. Mortality was not significantly different between SARS-CoV-2–positive KTR and non-KTR, but there was a notable trend toward higher mortality in SARS-CoV-2–positive KTR (25% versus 16%, $P=0.15$, respectively).

Conclusions Hospitalized SARS-CoV-2–positive KTR had a high rate of mortality and hospital complications, such as requiring ventilation, vasopressor use, and AKI. Additionally, they had higher odds of hospital complications compared with SARS-CoV-2–positive non-KTR after adjusting for Elixhauser score, Black race, and baseline eGFR. Future studies with larger sample size of KTR are needed to validate our findings.

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease (coronavirus disease 2019) was first identified in the Wuhan district of China in December, 2019, and was declared a global pandemic by the World Health Organization on March 11, 2020. The current patient count has exceeded 21 million people worldwide, with more than 760,000 deaths (1). The United States has emerged as the country with the highest number of infections in the world, with more than 5.2 million patients at this time (1). Although it is believed this virus can infect any potential human host, the kidney transplant recipient (KTR) population is considered more susceptible to severe infection on the basis of their ongoing treatment with immunosuppression and previous experience with other viral infections (2,3). For instance, it has been shown that influenza in transplant recipients has been associated with high rates of medical complications, and even mortality (3). Similarly, multiple other respiratory viral infections have also been shown to have worse outcomes in transplant recipients, as compared with the general population (2). In contrast, it has been observed that the hyperinflammatory phase in the setting of SARS-CoV-2 infection is associated with significant clinical deterioration and poor outcomes (4,5). Therefore, it is hypothesized that transplant recipients taking immunosuppression may be protected from this hyperinflammatory phase of coronavirus disease 2019 (6–10). However, research studies from the Brescia Task force, Columbia Transplant Center, the Post-Transplant

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Glomerular Diseases international consortium, and other centers have reported case fatality rates in SARS-CoV-2–positive transplant recipients in the range of 24%–35%, which is significantly higher than the estimated case fatality rates in the general population (9,11–15). The rates of AKI have varied from 33% to 52% with 20%–25% of these requiring RRT (11,13,15). Yet, these published studies did not have a control group or extrapolated comparative data from the wider population database (historical controls) (11–15).

Recently published literature from the STOP-COVID investigators and the Henry Ford group have provided more insight by comparing outcomes in patients who were SARS-CoV-2 positive and had a solid organ transplant (SOT), and SARS-CoV-2–positive non-SOT controls (16,17). Both groups reported similar mortality in the comparison groups; however, the former focused on patients who were critically ill after SOT, whereas the latter included all inpatients who underwent SOT. Both studies did not include a comparator group of transplant recipients who tested negative for SARS-CoV-2. A control group of KTRs who tested negative for SARS-CoV-2 would allow us to understand the attributable risk of the adverse outcomes that would be associated with coronavirus disease 2019. There remains a need to investigate the differences in coronavirus disease 2019 outcomes in all hospitalized KTR in comparison to other control groups, within the same hospital system and the same time frame to ensure exposure to similar treatment protocols. In an effort to address this gap in knowledge, we present the outcomes of inpatient SARS-CoV-2–positive KTR and contemporaneous control groups from the same institution, including SARS-CoV-2–positive non-KTR, SARS-CoV-2–negative KTR, and SARS-CoV-2–negative non-KTR.

Materials and Methods

We used the electronic health record data between March 4, 2010 and September 9, 2020 from six hospitals within the Yale New Haven Health System. We identified adult inpatients who were at least 18 years of age, and were tested for SARS-CoV-2 *via* nasopharyngeal RNA PCR swab 14 days preceding hospitalization, and up to the date of discharge. Using the International Classification of Disease 10 codes, we identified patients who were KTR within our dataset with code Z94.0 (18). SARS-CoV-2 positivity was defined as the first nucleic acid detection *via* the SARS-CoV-2 RNA nasopharyngeal swab.

This study was approved by the Yale human investigation committee (2000027733), operated under a waiver of informed consent, and was deemed minimal risk as medical record research. This study adhered to the Declaration of Helsinki.

Baseline Characteristics, Vital Signs, and Laboratory Measurements

Covariates of interest were extracted from the electronic health record, and included data on demographics, comorbidities, biochemical data, and vital signs. We calculated the Elixhauser comorbidity score using a validated administrative coding system (19). Given the longitudinal nature of our study design, and repeated measurements per observation, we summarized inpatient continuous variables (such as vital signs, and laboratory measurements) as the median of all available measurements per patient. Therefore, the median (interquartile) values presented in this study represent the median of the medians.

Operational Definitions of Outcomes

Our primary outcomes were intensive care unit (ICU) admission, use of mechanical ventilation, use of vasopressors, development of AKI, and inpatient mortality during index hospitalization. ICU admission was defined by manual mapping of location data for patients, and was independently validated through chart review. Ventilator use was defined by a procedure order placed for a patient consistent with ventilation orders, and vasopressors were defined by manual mapping of medications from the pharmacy formulary consistent with this class of medication. Medication use was defined as "yes" if the participant was ever exposed to the medication at index hospitalization. Hospital mortality was defined by structured discharge disposition data from the health record and was validated with chart review. We defined AKI using Kidney Disease: Improving Global Outcomes criteria of $\geq$0.3 mg/dl or 50% increase in creatinine from baseline. Baseline creatinine was defined as the median of the last three creatinine values obtained 7–365 days before hospital admission.

Statistical Analyses

Continuous variables were reported as median (interquartile range, IQR), and categorical variables were reported as frequencies, *n* (%). Differences in clinical and demographic characteristics were evaluated by the Kruskal-Wallis test or chi-squared test for continuous or categorical variables, respectively. We used logistic regression models to assess the associations between KTR who were SARS-CoV-2 positive with the primary outcomes of ICU admission, ventilator use, vasopressor use, development of AKI, and hospital mortality. The odds ratios (OR) and 95% confidence intervals (95% CI) of both the univariable and multivariable models (adjusting for Elixhauser comorbidity score, Black race, and baseline eGFR) are reported. All inference testing was two-sided with an alpha of 0.05. We constructed three logistic regression models. The first model evaluated associations between KTR status and outcomes among patients who were SARS-CoV-2 positive. The second model evaluated associations between SARS-CoV-2 status and outcomes among KTR. Finally, the third model evaluated the associations between SARS-CoV-2–positive KTR and outcomes compared with SARS-CoV-2–negative non-KTR. All models were adjusted for Elixhauser comorbidity score, Black race, and baseline eGFR. Analyses were conducted in SAS, version 9.4 (SAS Institute Inc).

Results

Baseline Characteristics

Overall, we included 31,540 patients, among whom 3213 (10%) tested positive for SARS-CoV-2 and 28,327 (90%) tested negative for SARS-CoV-2. Among those who tested positive for SARS-CoV-2, 32 (1%) were KTR, and among those who tested negative, 224 (0.8%) were KTR (Figure 1). The median age of all patients tested for SARS-CoV-2 was

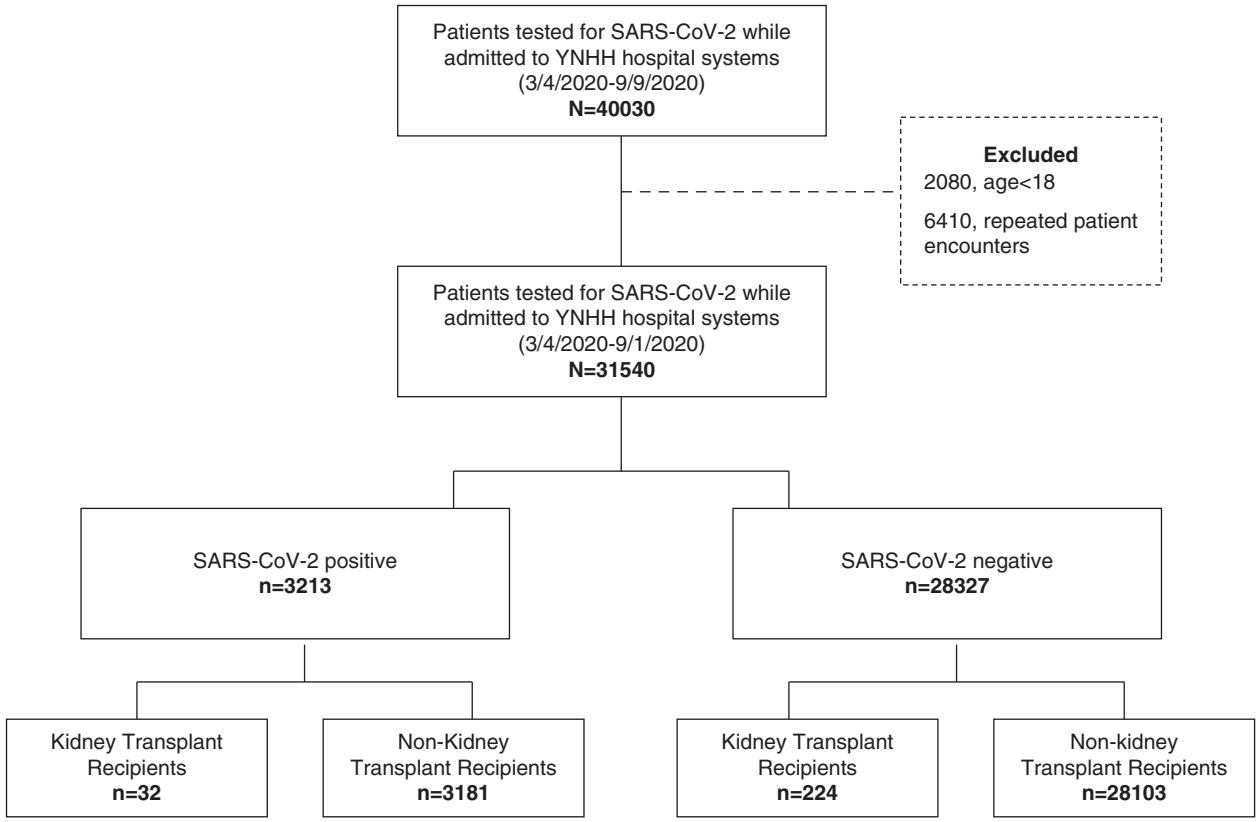

Figure 1. | **Study flow diagram.** SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; YNHH, Yale New Haven Hospital.

60 years (IQR, 38–74) years. Females made up 58% (18,135 out of 31,540) of the cohort, and 17% (5302 out of 31,540) were Black. The median Elixhauser comorbidity score was 4 (IQR, 1–8) with 28% (8743 out of 31,540) having diabetes, 55% (17,398 out of 31,540) with hypertension, 32% (10,001 out of 31,540) with chronic pulmonary disease, and 28% (8685 out of 31,540) with obesity. SARS-CoV-2–positive KTR had higher rates of Black participants, diabetes, stroke, and longer hospital stays as compared with all other control groups including SARS-CoV-2–positive non-KTR, and SARS-CoV-2–negative KTR and non-KTR (Table 1). Furthermore, SARS-CoV-2–positive KTR had a similar level of comorbidity to other KTR who were SARS-CoV-2 negative, but they had a significantly higher level of comorbidity as measured by Elixhauser score as compared with all non-KTR who were both SARS-CoV-2 positive and negative.

Distribution of Vital Signs and Biochemical Data

SARS-CoV-2–positive KTR had significantly higher peak BPs compared with all other control groups (Supplemental Table 1). On biochemical analysis, SARS-CoV-2–positive KTR had significantly higher median BUN (40.8; IQR, 24.5–56 versus 17.5; IQR, 12–28, $P<0.001$) and creatinine (2.1; IQR, 1.3–2.7 versus 0.9; IQR, 0.7–1.2, $P<0.001$) during their hospitalization as compared with SARS-CoV-2–positive non-KTR. SARS-CoV-2–positive KTR also had metabolic derangements associated with kidney dysfunction, such as lower bicarbonate (median 21.5; IQR,19.5–23.5 versus 24; IQR, 22–26, $P<0.001$) compared with non-KTR who were SARS-CoV-2 positive (Table 2). Furthermore, SARS-CoV-2–positive KTR had significantly lower median absolute lymphocyte count (0.7; IQR, 0.5–1 versus 1.2; IQR, 0.8–1.5, $P<0.001$) as shown in Table 2, and higher ferritin (median, 1412; IQR, 747.5–1748.5 versus 553; IQR, 256–1035, $P<0.001$) compared with SARS-CoV-2–positive non-KTR (Figure 2, Table 2). Ferritin remained significantly higher in the SARS-CoV-2–positive KTR group compared with non-KTR after adjusting for Elixhauser score (Supplemental Table 2). C-reactive protein, high sensitivity c-reactive protein, and d-dimer levels were not significantly different between SARS-CoV-2–positive KTR and non-KTR, although there was a trend toward higher d-dimer levels in the SARS-CoV-2–positive KTR group.

Rates of Hospital Complications

The overall rates of ICU admissions during the index hospitalization, ventilation, vasopressor use, AKI, and death were 20% (6287 out of 31,540), 6% (1850 out of 31,540), 12% (3799 out of 31,540), 9% (2882 out of 31,540), and 4% (1317 out of 31,540), respectively. SARS-CoV-2–positive KTR had significantly higher rates of ventilation, vasopressor use, and AKI compared with all other control groups, as shown in Table 3. SARS-CoV-2–positive KTR also had significantly higher rates of hospital mortality (25%) compared with SARS-CoV-2–negative KTR (2%) and SARS-CoV-2–negative non-KTR (3%), but not compared with SARS-CoV-2–positive non-KTR (16%, $P=0.15$). Additionally, SARS-CoV-2–positive KTR had about three times the

Table 1. Baseline characteristics

Baseline Characteristics	Patients	Controls			*P* values		
	Severe Acute Respiratory Syndrome Coronavirus 2 +/ Kidney Transplant Recipients, *N*=32	Severe Acute Respiratory Syndrome Coronavirus 2 +/ Nonkidney Transplant Recipients, *N*=3181	Severe Acute Respiratory Syndrome Coronavirus 2 −/ Kidney Transplant Recipients, *N*=224	Severe Acute Respiratory Syndrome Coronavirus 2 −/ Nonkidney Transplant Recipients, *N*=28,103	P^1	P^2	P^3
Age (yr), median (IQR)	61.5 (55.5–65.5)	65 (51–79)	59.5 (47–67)	59 (37–74)	0.18	0.22	0.44
Female, *n* (%)	14 (44)	1611 (51)	107 (48)	16,403 (58)	0.44	0.67	0.09
Black, *n* (%)	18 (56)	825 (26)	53 (24)	4406 (16)	<0.001	<0.001	<0.001
BMI (kg/m^2), median (IQR)	28.2 (23.8–30.7)	28.5 (24.4–33.9)	27.9 (23.3–32.3)	28.3 (24.2–33.3)	0.43	0.93	0.58
Obesity, *n* (%)	13 (41)	1033 (32)	87 (39)	7552 (27)	0.33	0.85	0.08
CHF, *n* (%)	15 (47)	697 (22)	83 (37)	5680 (20)	0.001	0.29	<0.001
Alcohol abuse, *n* (%)	3 (9)	287 (9)	20 (9)	3700 (13)	0.95	0.93	0.53
CPD, *n* (%)	10 (31)	1028 (32)	69 (31)	8894 (32)	0.90	0.96	0.96
Baseline eGFR, median (IQR)	37.4 (29.1–58.1)	76.8 (51.6–98.1)	31.5 (12.9–53.5)	79.6 (56.3–100.3)	<0.001	0.07	<0.001
Diabetes mellitus, *n* (%)	25 (78)	1254 (39)	129 (58)	7335 (26)	<0.001	0.03	<0.001
Hypertension, *n* (%)	31 (97)	2050 (64)	218 (97)	15,099 (54)	<0.001	0.88	<0.001
Liver disease, *n* (%)	12 (38)	343 (11)	68 (30)	3846 (14)	<0.001	0.42	<0.001
Malignancy, *n* (%)	3 (9)	360 (11)	39 (17)	4347 (15)	0.73	0.25	0.34
Stroke, *n* (%)	7 (22)	207 (7)	19 (8)	1659 (6)	0.001	0.02	<0.001
Elixhauser score, median (IQR)	10 (8–13.5)	5 (2–9)	10 (7–13)	4 (1–8)	<0.001	0.33	<0.001
Length of hospital stay (d), median (IQR)	10.2 (6.6–25.7)	7.9 (4.1–14.9)	4.8 (3.2–8.2)	3.3 (2.1–6.1)	0.01	<0.001	<0.001

P values were obtained using the Kruskal Wallis test. Values in red represent statistically significant differences. P1 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–positive non-KTR, P2 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–negative KTR, P3 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–negative non-KTR. IQR, interquartile range; BMI, body mass index; CHF, congestive heart failure; CPD, chronic pulmonary disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; KTR, kidney transplant recipient.

Table 2. Distribution of laboratory measurements among all groups

Median Laboratory Measurements	Patients	Controls			*P* values		
	Severe Acute Respiratory Syndrome Coronavirus 2 +/ Kidney Transplant Recipients, *N*=32, Median (Interquartile Range)	Severe Acute Respiratory Syndrome Coronavirus 2 +/ Nonkidney Transplant Recipients, *N*=3181, Median (Interquartile Range)	Severe Acute Respiratory Syndrome Coronavirus 2 −/ Kidney Transplant Recipients, *N*=224, Median (Interquartile Range)	Severe Acute Respiratory Syndrome Coronavirus 2 −/ Nonkidney Transplant Recipients, *N*=28,103, Median (Interquartile Range)	P^1	P^2	P^3
Basic metabolic panel							
Sodium, meq/L	141 (138.8–142)	139 (137–141)	137.8 (135.5–140)	139 (136.5–140.5)	0.01	<0.001	0.001
Potassium, meq/L	4.4 (3.9–4.6)	4 (3.8–4.3)	4.3 (3.9–4.6)	4 (3.8–4.3)	0.001	0.86	<0.001
Chloride, meq/L	105.3 (102–107.8)	102.5 (100–105.5)	103 (99–106)	104 (101–106)	0.007	0.03	0.07
Bicarbonate, meq/L	21.5 (19.5–23.5)	24 (22–26)	21.8 (19.3–23)	24 (22–26)	<0.001	0.83	<0.001
BUN, mg/dl	40.8 (24.5–56)	17.5 (12–28)	34.8 (21–52)	15.5 (11–23)	<0.001	0.41	<0.001
Creatinine, mg/dl	2.1 (1.3–2.7)	0.9 (0.7–1.2)	2 (1.3–4.5)	0.9 (0.7, 1.2)	<0.001	0.30	<0.001
Albumin, g/dl	3 (2.8, 3.4)	3.2 (2.9, 3.6)	3.5 (3.1, 4)	3.5 (3.1–4)	0.15	<0.001	<0.001
Complete blood count							
WBC, 1000/uL	5.7 (4.4–8.1)	6.5 (4.9–9.0)	7.6 (5.3–10.9)	9.0 (6.8–11.5)	0.21	0.05	<0.001
Hemoglobin, g/dl	10.5 (8.6–12.2)	12 (10.4–13.3)	10.2 (8.8–11.8)	11.7 (10.2–13.1)	<0.001	0.93	0.001
Platelets, 1000/μl	190.8 (161–248)	226 (173.5–293)	184 (132.8–232)	213 (167–265.5)	0.01	0.56	0.12
ALC, 1000/μl	0.7 (0.5–1)	1.2 (0.8–1.5)	0.7 (0.3–1.2)	1.5 (1.1–2)	<0.001	0.52	<0.001
ANC, 1000/μl	4.3 (2.6–6.1)	4.4 (3–6.7)	6 (3.9–8.8)	6.3 (4.4–8.7)	0.59	0.03	0.001
Inflammatory markers							
Ferritin, ng/ml	1412 (747.5–1748.5)	553 (256–1035)			<0.001		
CRP, mg/dl	4.3 (1.6–11)	6.1 (1.9–11)			0.75		
hsCRP, mg/L	45.3 (14.3–92.3)	44.6 (13–86.3)			0.89		
D-dimer, μg/ml	1.7 (1–2.8)	1.2 (0.7–2.5)			0.07		

P values were obtained using the Kruskal-Wallis test. Values in red represent statistically significant differences. P1 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–positive non-KTR, P2 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–negative KTR, P3 tests the difference between SARS-CoV-2 positive KTR and SARS-CoV-2 negative non-KTR. WBC, white blood cell; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, c-reactive protein; hsCRP, high sensitivity c-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; KTR, kidney transplant recipients.

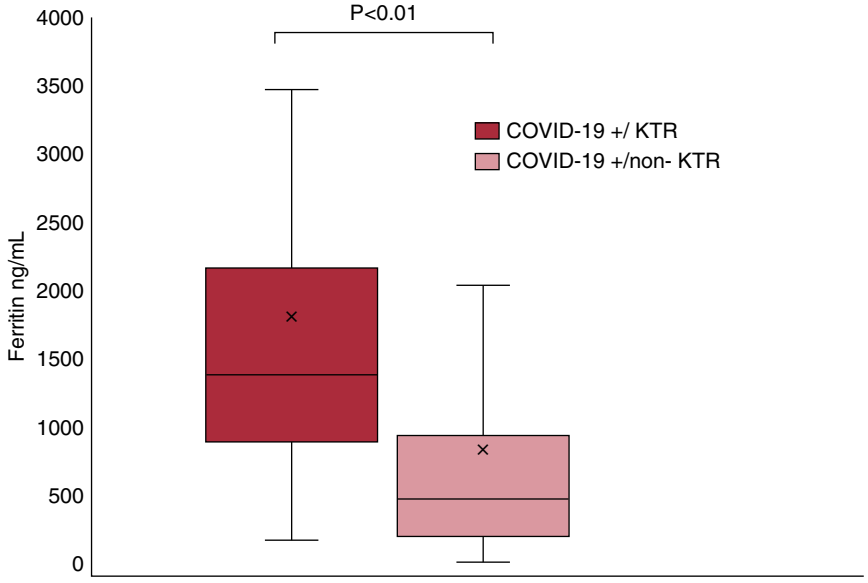

Figure 2. | Distribution of ferritin among patients who were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive. SARS-CoV-2–positive kidney transplant recipients (KTR) (represented in dark red) have significantly higher ferritin levels compared with SARS-CoV-2–positive non-KTR (represented in light red). The boxplot shows the mean, represented by the "X"; median, represented by the horizontal line inside the box; interquartile range represented by the outer bounds of the box; minimum and maximum data points excluding outliers, represented by the whiskers.

odds of requiring mechanical ventilation compared with SARS-CoV-2–positive non-KTR (OR, 3.31; 95% CI, 1.59 to 6.89) independent of Elixhauser comorbidity score, Black race, and baseline eGFR as shown in Figure 3. SARS-CoV-2–positive KTR also had 2.3 times the odds of requiring vasopressors (OR, 2.32; 95% CI, 1.12 to 4.80) and 2.5 times the odds of developing AKI (OR, 2.48; 95% CI, 1.17 to 5.29) independent of Elixhauser score, Black race, and baseline eGFR. The relationship between SARS-CoV-2 infection and the outcomes of vasopressor use and mechanical ventilation are significantly modified by kidney transplant status, as shown by the interaction *P* values in Table 3. Similar associations were identified when comparing the outcomes of mechanical ventilation, vasopressor use, and AKI in SARS-CoV-2–positive KTR with SARS-CoV-2–negative KTR and non-KTR (Supplemental Tables 3 and 4). In addition, mortality rates were significantly higher in SARS-CoV-2–positive KTR compared with SARS-CoV-2–negative KTR and SARS-CoV-2–negative non-KTR, after adjusting for Elixhauser comorbidity score, Black race, and baseline eGFR (Supplemental Tables 3 and 4).

Distribution of Coronavirus Disease 2019–Related Pharmacotherapy and Immunosuppressive Medications

There were some differences in the management of patients who were SARS-CoV-2 positive between KTR and non-KTR, with more patients who were KTR receiving hydroxychloroquine and tocilizumab than non-KTR, with a trend toward higher use of methylprednisolone (Table 4). Additionally, among KTR there were some differences in immunosuppression use, with significantly lower use of mycophenolate in SARS-CoV-2–positive KTR compared with SARS-CoV-2–negative KTR, as shown in Table 5. Details of type and timeline of kidney transplantation and induction therapy in SARS-CoV-2–positive KTR is provided in Supplemental Table 5. We also compared tacrolimus levels in KTRs who are SARS-CoV-2 positive with and without hospital complications (Supplemental Table 6), and we identified there were lower median tacrolimus levels in recipients with hospital complications.

Discussion

In this study we evaluated hospital outcomes in SARS-CoV-2–positive KTR. We identified that SARS-CoV-2–positive KTR had a higher risk of hospital complications such as mechanical ventilation, vasopressor use, and development of AKI compared with other patients who were SARS-CoV-2 positive and SARS-CoV-2 negative. Hospitalized SARS-CoV-2–positive KTR had a high rate of mortality at 25%. There was a higher rate of mortality in SARS-CoV-2–positive KTR compared with SARS-CoV-2–negative KTR and non-KTR. Although there was no significant difference in mortality between SARS-CoV-2–positive KTR (25%) and SARS-CoV-2–positive non-KTR (16%), there was a notable trend toward higher mortality in SARS-CoV-2–positive KTR. Our results add to the existing body of literature showing that SARS-CoV-2–positive KTR have more hospital complications compared with non-KTR infected with SARS-CoV-2, but our findings also identified that these complications are independent of comorbidities, Black race, and baseline eGFR, and remain higher in comparison to SARS-CoV-2–negative KTR and non-KTR (9,11–15).

Our study further explored differences in laboratory measurements and vital signs between SARS-CoV-2–positive KTR and SARS-CoV-2–positive non-KTR, and

Table 3. Distribution of hospital complications among patients tested for severe acute respiratory syndrome coronavirus 2

Hospital Complications	Total N=31,540, n (%)	Patients	Controls			P values			
		Severe Acute Respiratory Syndrome Coronavirus 2 +/ Kidney Transplant Recipients, N=32, n (%)	Severe Acute Respiratory Syndrome Coronavirus 2 +/Non-Kidney Transplant Recipients, N=3181, n (%)	Severe Acute Respiratory Syndrome Coronavirus 2 −/ Kidney Transplant Recipients, N=224, n (%)	Severe Acute Respiratory Syndrome Coronavirus 2 −/Non-Kidney Transplant Recipients, N=28,103, n (%)	P^1	P^2	P^3	$P^{\text{Interaction}}$
ICU admission	6287 (20)	11 (34)	766 (24)	55 (25)	5455 (19)	0.18	0.24	0.03	0.37
Ventilation	1850 (6)	11 (34)	437 (14)	20 (9)	1382 (5)	<0.001	<0.001	<0.001	0.05
Vasopressor use	3799 (12)	13 (41)	503 (16)	37 (17)	3246 (12)	<0.001	0.001	<0.001	0.01
AKI	2882 (9)	15 (47)	458 (15)	51 (23)	2358 (10)	<0.001	0.004	<0.001	0.07
Inpatient mortality	1317 (4)	8 (25)	498 (16)	5 (2)	806 (3)	0.15	<0.001	<0.001	0.12

P values were obtained using the Kruskal-Wallis test. Values in red represent statistically significant differences. P1 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–positive non-KTR, P2 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–negative KTR, P3 tests the difference between SARS-CoV-2–positive KTR and SARS-CoV-2–negative non-KTR, and PInteraction tests the interaction between SARS-CoV-2 and KTR status (a significant interaction P value can be interpreted as the relationship between SARS-CoV-2 infection and outcome is significantly modified by kidney transplant status). ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; KTR, kidney transplant recipient.

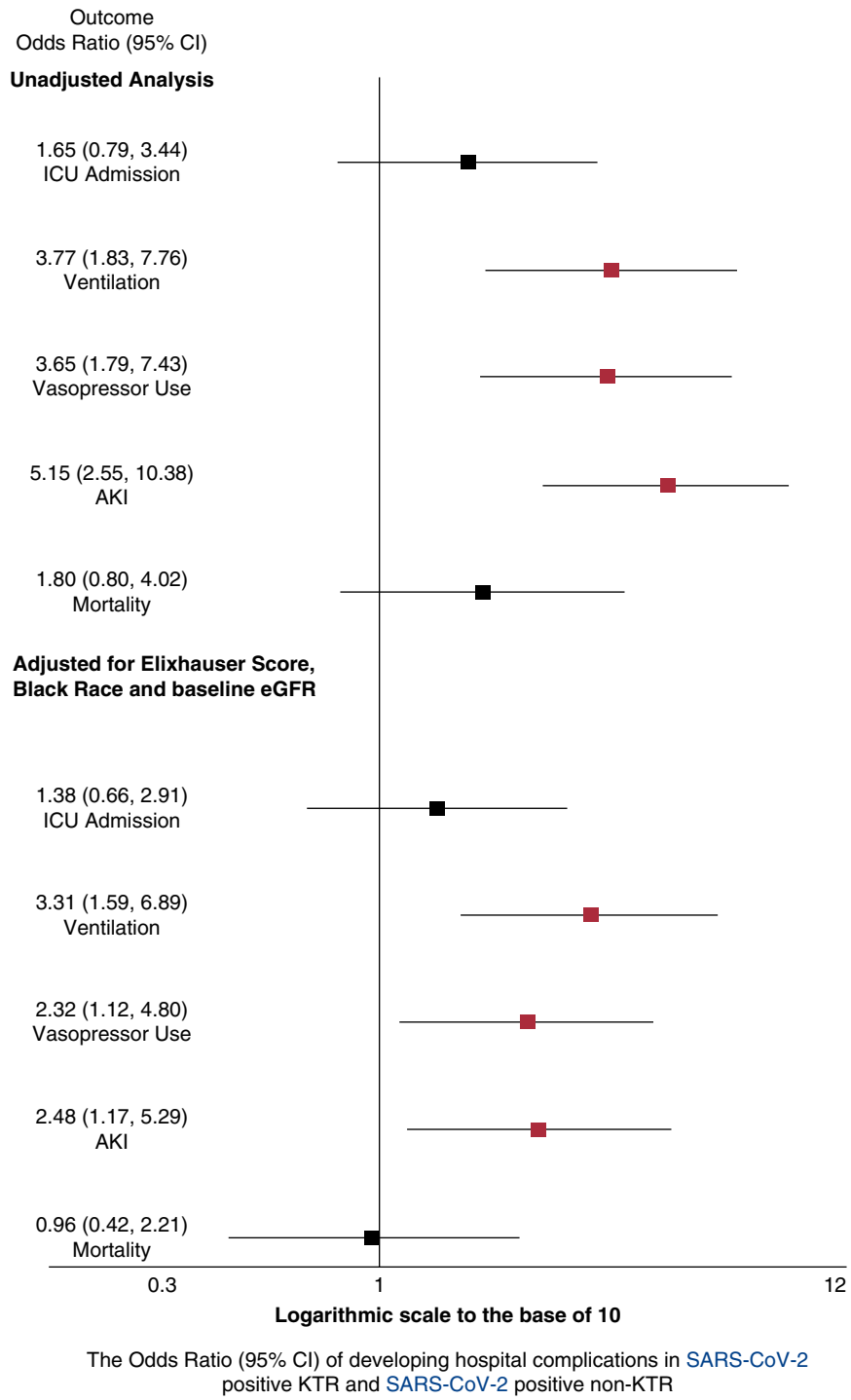

Figure 3. | Forest plot of the odds ratio of hospital complications in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive kidney transplant recipients (KTR) compared with SARS-CoV-2–positive non-KTR. The forest plot shows SARS-CoV-2–positive KTR have significantly higher odds of mechanical ventilation, vasopressor use, and AKI independent of Elixhauser score, Black race, and baseline eGFR. The squares represent the odds ratio and the lines represent the 95% confidence intervals. Significant associations are represented in red and nonsignificant associations are in black. The x-axis uses a logarithmic scale to the base of 10. The above associations are the unadjusted analyses, and the bottom associations are adjusted for Elixhauser score, Black race, and baseline eGFR.

patients who were SARS-CoV-2 negative. SARS-CoV-2–positive KTR portrayed a more severe clinical profile with higher BPs, more severe metabolic acidosis, and lower kidney function. Furthermore, SARS-CoV-2–positive KTR had more severe elevations in inflammatory markers, such as ferritin. Although elevations in ferritin may be confounded by pre-existing history of anemia in KTR, these elevations remained significant even after adjusting for the level of

Table 4. Distribution of coronavirus disease 2019 treatment

Treatment	Total, N=3213, n (%)	Severe Acute Respiratory Syndrome Coronavirus 2 Positive		P value
		Kidney Transplant Recipients, N=32, n (%)	Non-Kidney Transplant Recipients, N=3181, n (%)	
Hydroxychloroquine	2136 (66)	27 (84)	2109 (66)	0.03
Tocilizumab	1275 (40)	21 (66)	1254 (39)	0.003
Methylprednisolone	611 (19)	10 (31)	601 (19)	0.08
Remdesivir	309 (10)	2 (6)	307 (10)	0.52
Azithromycin	618 (19)	6 (19)	612 (19)	0.94

P values were obtained using the Kruskal-Wallis test. Values in red represent statistically significant differences. Fisher's exact test was used for comparison in cells with < five participants.

Table 5. Maintenance immunosuppression among kidney transplant recipients with and without severe acute respiratory syndrome coronavirus 2 while an inpatient

Immunosuppression	Total, N=256, n (%)	Kidney Transplant Recipients		P value
		Severe Acute Respiratory Syndrome Coronavirus 2 Positive, N=32, n (%)	Severe Acute Respiratory Syndrome Coronavirus 2 Negative, N=224, n (%)	
Tacrolimus	195 (76)	27 (84)	168 (75)	0.24
Belatacept	16 (6)	2 (6)	14 (6)	1.00
Cyclosporine	12 (5)	1 (3)	11 (5)	0.66
Sirolimus	7 (3)	0 (0)	7 (3)	0.60
Everolimus	5 (2)	0 (0)	5 (2)	1.00
Mycophenolate	152 (59)	11 (34)	141 (63)	0.002
Azathioprine	14 (5)	2 (6)	12 (5)	0.69
Steroids	219 (86)	26 (81)	193 (86)	0.46

P values were obtained using the Kruskal-Wallis test. Values in red represent statistically significant differences. Fisher's exact test was used for comparison in cells with < five participants.

comorbidity. The elevations in ferritin and a trend of higher levels of d-dimer offer further support against the notion that chronic treatment with immunosuppressive medications may attenuate the inflammatory phase associated with SARS-CoV-2 infection (20–22).

To our knowledge, this study is first to utilize multiple comparison groups with a large sample size from the same institution and the same time frame. Our cohort included patients from six hospitals, both community-level and academic-level hospitals, which enhances the generalizability of our findings to different inpatient settings. Additionally, all patients who were SARS-CoV-2 positive were systematically treated with a standard protocol for using antiviral drugs, IL-6 inhibitors, and other potential treatments, thus making them more comparable for assessing outcomes. Despite these standard protocols, there was a higher use of hydroxychloroquine and tocilizumab in KTR, which likely reflects the severity of illness in SARS-CoV-2–positive KTR. Furthermore, we identified a notable trend toward higher mortality in SARS-CoV-2–positive KTR (25%) compared with SARS-CoV-2–positive non-KTR (16%), despite the trend toward higher use of corticosteroids, which has been shown to decrease mortality in patients with severe respiratory illness secondary to coronavirus disease 2019 in the Randomized Evaluation of COVID-19 Therapy trial (23). Our study timeline also captures both the ascending and peak time periods of the coronavirus pandemic, and therefore our hospital complications and mortality rates more accurately reflect the temporal changes associated with coronavirus disease 2019. Furthermore, we evaluated our hospital complications and mortality outcomes independent of Elixhauser comorbidity score, Black race, and baseline eGFR (19). The Elixhauser score has previously been validated and was significantly associated with in-hospital mortality and health service measures associated with burden of illness in prior studies (19,24).

It is important to note that our findings differed from two recently published studies with comparator groups. We identified that transplant status in the setting of SARS-CoV-2 infection is linked to worse hospital outcomes, but not mortality, whereas Chaudhry *et al.* (17) found no difference between SOT recipients and nonrecipients with regard to a composite outcome of ICU care, mechanical ventilation, and all-cause mortality. The variability in our findings is likely due to differences in sample size and cohort characteristics. Chaudhry *et al.* reported on 100 patients in the control group who were nontransplant recipients infected with SARS-CoV-2, of which 80% were Black, compared with only 26% in our control group of 3181 SARS-CoV-2–infected non-transplant recipients. However, in our cohort, even after adjusting for Black race, SARS-CoV-2–positive KTR still had higher odds of hospital complications. Our findings are also in contrast to the recently published work by the STOP-COVID investigators, which did not find differences in outcomes between SARS-CoV-2–positive transplant and nontransplant recipients (15). This is also partly due to our cohort differences, as we did not limit our cohort to patients in the ICU. This may be a key difference as the subset of patients who were non-KTR that are admitted to the ICU are substantially sicker than patients managed on the medical wards, which is evident in our mortality rate of 16% in SARS-CoV-2–positive non-KTR compared with a rate of 43% in SARS-CoV-2–positive nontransplant recipients, as reported by Molnar *et al.* (15)

A large variable that separates patients who undergo kidney transplant from the general population is the use of immunosuppression. Despite multiple publications, the role of immunosuppression in the clinical course of coronavirus disease 2019 has remained unclear (7,8). Although, on one hand, due to immunosuppression, KTRs are theoretically at higher risk of acquiring this infection and having a less favorable course, on the other hand, immunosuppression could play a protective role against the inflammatory phase of this disease (6–9). In our cohort, we could not identify a trend toward less inflammation in patients who are KTR and infected with SARS-CoV-2. In fact, KTR had higher levels of ferritin compared with non-KTR infected with SARS-CoV-2. Although some *in-vitro* studies suggest a potential antiviral effect of cyclosporine, tacrolimus, and mycophenolate (25), there have been no human trials to support this potential benefit. Our findings suggest that transplant status is linked to higher hospital complications, which may be due to immunosuppression, but this question was not answered by our study (20,26). Furthermore, we identified lower median tacrolimus levels in SARS-COV-2–positive KTR who required ventilation, vasopressor use, and ICU admission. However, it is likely clinicians stopped or lowered immunosuppression dosing in patients with more severe clinical presentation.

Our KTR population infected with SARS-CoV-2 had a lower rate of mycophenolate use compared with other KTR who were SARS-CoV-2 negative. The clinical relevance of this difference in immunosuppression and effect on outcomes remains unclear. It is also important to note these differences in immunosuppression are heavily influenced by clinical judgment. Immunosuppression management within the Yale New Haven Health System typically included the removal of the antimetabolite/secondary agent and the calcineurin inhibitor/primary agent was adjusted on the basis of the severity of the illness in patients infected by SARS-CoV-2. Steroids were routinely continued, and the use of methylprednisolone was on the basis of the severity of lung involvement and was decided on in conjunction with the intensive care and infectious disease clinicians. Hence, the role of immunosuppression in coronavirus disease 2019 outcomes needs to be interpreted with caution, because it may be a marker of the severity of illness and more reflective of clinical management, rather than offer insight into the causal pathway of coronavirus disease 2019 outcomes in KTR. Furthermore, our data were limited in capturing cumulative dose of immunosuppression, because our definition of medication use was on the basis of any exposure of immunosuppression while an inpatient.

We also found a significantly higher incidence of liver disease in the SARS-CoV-2 KTR compared with both the SARS-CoV-2–negative cohorts. Whether liver disease is a risk factor for coronavirus disease 2019 is uncertain on the basis of the current literature (27), and this finding may be reflective of underlying nonalcoholic fatty acid liver disease in the setting of significantly higher incidence of diabetes in the SARS-CoV-2–positive KTR.

Our findings need to be interpreted in the context of our study's limitations. Although we have a large sample size,

with multiple comparison groups, our study is still limited to a single geographical location, and hence our results may only be generalizable to other populations with similar demographics. Given the smaller number of participants with KTR and SARS-CoV-2 infection from a single hospital network, we were limited in how many confounders we could adjust for in our associative analyses, and therefore our identified associations need to be validated in a larger multicenter cohort of SARS-CoV-2–positive KTR. We used Elixhauser score in our multivariable model, which is limited by the use of ICD codes to calculate the comorbidity score. Additionally, we identified patients who were tested for SARS-CoV-2 anywhere from 14 days before admission to time of discharge. This may have included patients who were asymptomatic being tested for discharge planning or before surgery, which may have decreased the severity of illness in our cohort. Nonetheless, we would expect this bias to nondifferentially affect all groups.

In conclusion, hospitalized SARS-CoV-2–positive KTR had a high rate of mortality and hospital complications. Additionally, SARS-CoV-2–positive KTR had higher rates of hospital complications compared with SARS-CoV-2–positive non-KTR, independent of the level of comorbidities, Black race, and baseline eGFR. Although these findings need to be validated in larger studies, they may help inform discussions between KTR and their physicians regarding the severity of coronavirus illness in the kidney transplant population.

Disclosures

E. Marin reports having consultancy agreements with Natera and Veloxis; reports being a scientific advisor or member of the *Kidney360* Review Board; and reports having other interests/relationships as a member of the American Society of Nephrology and American Society of Transplantation. D. Moledina reports a patent to Systems and Methods to Diagnose Acute Interstitial Nephritis pending. F. Wilson reports having consultancy agreements with Translational Catalyst, LLC; reports having an ownership interest in Efference, LLC; reports being a scientific advisor or member of the Editorial Board of the *American Journal of Kidney Disease* and the Editorial Board of *CJASN*; and reports other interests/relationships as Board of Directors of Gaylord Health Care and Medical Commentator of Medscape. All remaining authors have nothing to disclose.

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Author Contributions

J.H. Greenberg, D. Malhotra, S.G. Mansour, E. Marin, D.G. Moledina, and F.P. Wilson conceptualized the study; S.G. Mansour, M. Simonov, and Y. Yamamoto were responsible for the formal analysis; S.G. Mansour and E. Marin were responsible for the investigation; J. Alausa, T. Arora, J.H. Greenberg, D. Malhotra, S.G. Mansour, E. Marin, D.G. Moledina, M. Simonov, L. Subair, and F.P. Wilson were responsible for the methodology; S.G. Mansour and F.P. Wilson were responsible for the visualization; D. Malhotra and S.G. Mansour were responsible for writing the original draft; M. Simonov and F.P. Wilson were responsible for the resources; J. Alausa, T. Arora, M. Simonov, L. Subair, F.P. Wilson, and Y. Yamamoto were responsible for the data curation; E. Marin and F.P. Wilson provided the supervision; F.P. Wilson was responsible for the funding acquisition and validation; and all authors reviewed, edited, and approved the final version of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0005652020/-/DCSupplemental.

Supplemental Table 1. Distribution of vital signs among SARS-CoV-2–tested patients.

Supplemental Table 2. Associations between SARS-CoV-2–positive KTR and inflammatory markers as compared with SARS-CoV-2–positive non-KTR.

Supplemental Table 3. Associations between SARS-CoV-2–positive KTR and hospital complications as compared with SARS-CoV-2–negative KTR.

Supplemental Table 4. Associations between SARS-CoV-2–positive KTR and hospital complications as compared with SARS-CoV-2–negative non-KTR.

Supplemental Table 5. Type and timeline of kidney transplantation and induction therapy in SARS-CoV-2–positive kidney transplant recipients.

Supplemental Table 6. Comparison of tacrolimus levels in kidney transplant recipients who are SARS-CoV-2 positive with and without outcomes.

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