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## Outcomes of patients with end-stage kidney disease hospitalized with COVID-19.

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# Outcomes of patients with end-stage kidney disease hospitalized with COVID-19

Q2Q1

Q19 Jia H. Ng<sup>1,5</sup>, Jamie S. Hirsch<sup>1,2,3,5</sup>, Rimda Wanchoo<sup>1</sup>, Mala Sachdeva<sup>1</sup>, Vipulbhai Sakhiya<sup>1</sup>, Susana Hong<sup>1</sup>, Kenar D. Jhaveri<sup>1</sup> and Steven Fishbane<sup>1</sup>; on behalf of the Northwell COVID-19 Research Consortium and the Northwell Nephrology COVID-19 Research Consortium<sup>4</sup>

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**Given the high risk of infection-related mortality, patients with end-stage kidney disease (ESKD) may be at increased risk with COVID-19. To assess this, we compared outcomes of patients with and without ESKD, hospitalized with COVID-19. This was a retrospective study of patients admitted with COVID-19 from 13 New York hospitals from March 1, 2020, to April 27, 2020, and followed through May 27, 2020. We measured primary outcome (in-hospital death), and secondary outcomes (mechanical ventilation and length of stay). Of 10,482 patients with COVID-19, 419 had ESKD. Patients with ESKD were older, had a greater percentage self-identified as Black, and more comorbid conditions. Patients with ESKD had a higher rate of in-hospital death than those without (31.7% vs 25.4%, odds ratio 1.38, 95% confidence interval 1.12 - 1.70). This increase rate remained after adjusting for demographic and comorbid conditions (adjusted odds ratio 1.37, 1.09 - 1.73). The odds of length of stay of seven or more days was higher in the group with compared to the group without ESKD in both the crude and adjusted analysis (1.62, 1.27 - 2.06; vs 1.57, 1.22 - 2.02, respectively). There was no difference in the odds of mechanical ventilation between the groups. Independent risk factors for in-hospital death for patients with ESKD were increased age, being on a ventilator, lymphopenia, blood urea nitrogen and serum ferritin. Black race was associated with a lower risk of death. Thus, among patients hospitalized with COVID-19, those with ESKD had a higher rate of in-hospital death compared to those without ESKD.**

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KEYWORDS: COVID-19; ESKD; ESRD; dialysis; hemodialysis; peritoneal dialysis

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<sup>5</sup>JHN and JSH are co-lead authors and contributed equally.

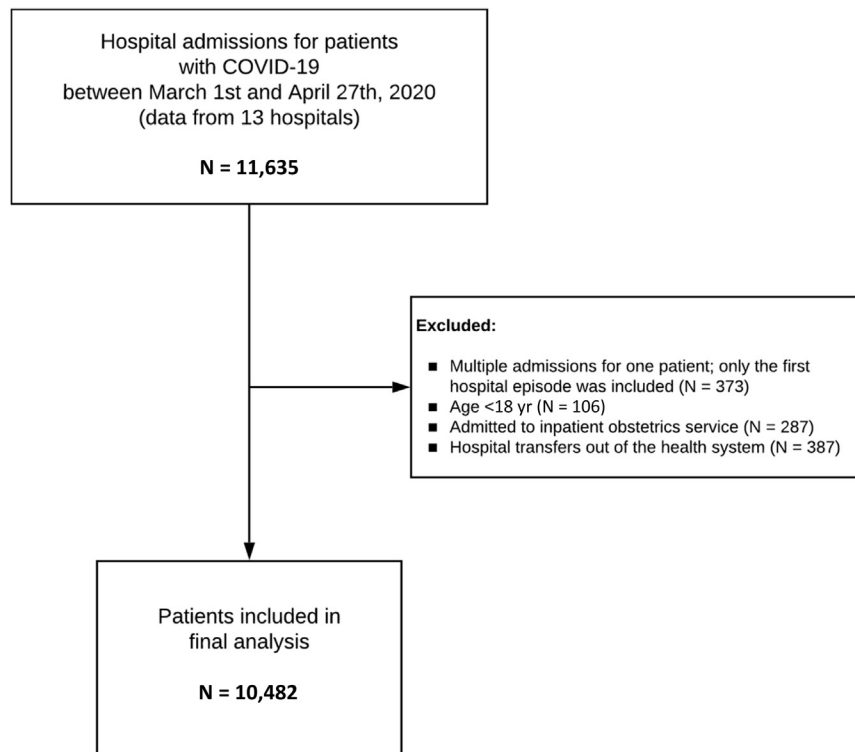
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A novel coronavirus, severe acute respiratory syndrome (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged in late 2019 in Wuhan, China, and rapidly spread throughout the world.<sup>1,2</sup> The disease has resulted in a large number of hospitalizations and intensive care unit (ICU) admissions, with now well-described pulmonary, cardiac, vascular, and renal complications.<sup>3-7</sup> To what degree COVID-19 has impacted patients with end-stage kidney disease (ESKD) on dialysis has not been fully elucidated. Understanding the outcomes of COVID-19-infected patients with and without ESKD is important because this information would help risk-stratify patients with ESKD to certain therapies for COVID-19 as they arrive at the hospital.

Patients with ESKD have a dysregulated immune system<sup>8</sup> and carry significant comorbid conditions, such as diabetes mellitus (DM), cardiac disease, and obesity, which are now considered risk factors for severe COVID-19 disease.<sup>9,10</sup> The ESKD population has higher annual mortality rates compared with the general population, even after adjustment for age, race, and DM. For example, annual mortality secondary to sepsis is 30–45 times higher in the dialysis population compared to the general population.<sup>11</sup> A recent study found an association between community influenza-like illness activity and seasonal variation in all-cause mortality among patients with ESKD, with an excess mortality of 1100 deaths per year, or 1.5%–2% of all deaths per influenza season in the ESKD cohort.<sup>12</sup> Despite recent improvements in mortality among patients with ESKD, with a 28% decline over the past 16 years, the ESKD population has a higher mortality rate compared with the general population, even after adjusting for age, race, and DM.<sup>13</sup>

With COVID-19, either an increased or decreased risk of death related to SARS-CoV-2 infection in ESKD could have been postulated. Severe disease with COVID-19 has been attributed to direct viral damage as well as the body's exuberant immune response.<sup>14</sup> Thus, the diminished immune response in ESKD could potentially protect against the cytokine storm observed with severe COVID-19 infection. In fact, in a preprint study published by Ma *et al.*, measured



**Figure 1 | Flowchart of study cohort.**

levels of inflammatory cytokines in dialysis patients with COVID-19 were found to be lower than those in other patients.<sup>15</sup> Another factor to consider is the reduced angiotensin-converting enzyme 2 (ACE2) activity seen in dialysis patients.<sup>16,17</sup> As ACE2 serves as a receptor that allows the novel coronavirus CoV-2 to enter a cell,<sup>18</sup> diminished activity could plausibly mitigate the severity of illness. Alternatively, patients on dialysis may be more susceptible to SARS-CoV-2 infection because of increased transmissibility in dialysis units and diminished ability to fight infection.<sup>19,20</sup>

To date, no large study exists on the outcomes of patients with ESKD who are hospitalized with COVID-19. Recent studies from China and Europe on patients with ESKD who were infected with COVID-19 have been limited to small numbers and single centers.<sup>21–24</sup> A single-center study from the United States (US) published recently also showed poor outcomes among 59 patients with ESKD—18 (31%) had died within the whole cohort, and 6 (75%) had died within the subset of patients requiring mechanical ventilation.<sup>25</sup> In the current study, we compared the outcomes of patients with and without ESKD among those hospitalized with COVID-19, and examined the risk factors associated with death in the non-ESKD group and in the ESKD group.

## RESULTS

From March 1, 2020 to April 27, 2020, there were 11,635 hospital admissions to 13 health system hospitals with a diagnosis of COVID-19 present on admission or made during the hospitalization. Of these, 10,482 were included in the final

cohort (Figure 1) and were followed through May 27, 2020. Of the included cohort, 7624 (72.7%) were discharged home, 2684 (25.6%) died, and 174 (1.7%) were still admitted. Within the cohort, 7346 (73%) patients in the non-ESKD group were discharged home, and 278 (66.3%) in the ESKD group.

A total of 419 (4.0%) patients with ESKD were treated in the hospital for COVID-19, of whom 408 (97.4%) were on hemodialysis (HD) and 11 (2.6%) were on peritoneal dialysis (Table 1). Within the HD group, 335 (82.1%) had permanent vascular access with either an arteriovenous graft or arteriovenous fistula, and 73 (17.9%) had an HD catheter. The baseline characteristics comparing patients with and without ESKD at hospital admission are provided in Table 1. Between the 2 groups, patients with ESKD were older, more frequently self-identified as Black, had lower body mass index (BMI), and were more likely to have Medicare as primary insurance. Additionally, patients with ESKD had more home medications, and a greater proportion were on antihypertensives, antiplatelets, anticoagulants, and statins. Patients with ESKD also had a higher proportion of comorbid diagnoses of DM, hypertension (HTN), coronary artery disease, peripheral vascular disease, and heart failure. During the hospital course, the severity of illness in both groups was similar in terms of ICU stay and vasopressor use. The in-hospital medications used to treat COVID-19 in the 2 groups are shown in Supplementary Table S1.

Patients with ESKD had a higher rate of in-hospital death than those without ESKD (31.7% vs. 25.4%; odds ratio [OR] 1.38, 95% confidence interval [CI] 1.12–1.70). After adjusting

**Table 1 | Demographic and clinical characteristics of patients with and without end-stage kidney disease**

Variables <sup>a</sup>	Non-ESKD (n = 10,063)	ESKD (n = 419)
Age at admission, yr	66 (54, 77)	66 (55, 75)
Age, y		
<40	729 (7.2)	25 (6.0)
40–49	1018 (10.1)	35 (8.4)
50–59	1878 (18.7)	74 (17.7)
60–69	2273 (22.6)	123 (29.4)
70–79	2096 (20.8)	104 (24.8)
≥80	2069 (20.6)	58 (13.8)
Male	5979 (59.4)	260 (62.1)
Race/Ethnicity		
Hispanic	2096 (20.8)	87 (20.8)
Non-Hispanic Black	1991 (19.8)	152 (36.3)
Non-Hispanic White	3476 (34.5)	93 (22.2)
Other	1783 (17.7)	69 (16.5)
Unknown	717 (7.1)	18 (4.3)
Insurance		
Commercial	3104 (30.8)	37 (8.8)
Medicaid	2042 (20.3)	81 (19.3)
Medicare	4677 (46.5)	299 (71.4)
Self-pay	121 (1.2)	0 (0.0)
Other	119 (1.2)	2 (0.5)
Tertiary hospital	6783 (67.4)	303 (72.3)
BMI, kg/m <sup>2</sup>	28.3 (25.0, 32.6)	26.5 (23.3, 31.2)
Missing	1101 (10.9%)	20 (4.8%)
Tobacco status		
Never	7433 (73.9)	308 (73.5)
Smoker	2013 (20.0)	88 (21.0)
Missing	617 (6.1)	23 (5.5)
Diabetes	3588 (35.7)	248 (59.2)
Hypertension	5966 (59.3)	382 (91.2)
CAD	1299 (12.9)	121 (28.9)
Heart failure	818 (8.1)	102 (24.3)
PVD	235 (2.3)	38 (9.1)
Asthma	828 (8.2)	31 (7.4)
COPD	629 (6.3)	34 (8.1)
Liver disease	277 (2.8)	16 (3.8)
Cancer	778 (7.7)	36 (8.6)
Chronic kidney disease	506 (5.0)	—
Dialysis modality		
Hemodialysis	—	408 (97.4)
Peritoneal dialysis	—	11 (2.6)
Dialysis modality access		
Permanent vascular access	—	335 (80.0)
Dialysis catheter	—	73 (17.4)
Peritoneal dialysis catheter	—	11 (2.6)
No. of medications	5.0 (1.0, 9.0)	9.0 (7.0, 14.0)
Type of medications		
ACE inhibitor	1277 (13.9)	38 (9.6)
ARB	1638 (17.8)	59 (14.9)
Anticoagulants	900 (9.8)	63 (15.9)
Antiplatelets	2442 (26.6)	195 (49.2)
Missing	877 (8.7)	23 (5.5)
No. of antihypertensives		
0	4064 (40.4)	60 (14.3)
1–2	3881 (38.6)	209 (49.9)
≥3	1241 (12.3)	127 (30.3)
Missing	877 (8.7)	23 (5.5)
Laboratory test results		
within 48 h of admission		
Hemoglobin, g/l	13.3 (12.0, 14.5)	10.5 (9.3, 11.5)

**Table 1 | (Continued)**

Variables <sup>a</sup>	Non-ESKD (n = 10,063)	ESKD (n = 419)
White blood cell count, 1000/μl	7.5 (5.6, 10.2)	6.3 (4.5, 8.6)
Lymphocyte count, 1000/μl	0.9 (0.6, 1.3)	0.7 (0.5, 1.1)
Neutrophil count, 1000/μl	5.8 (4.1, 8.4)	4.8 (3.2, 7.0)
Blood urea nitrogen, mg/dl	18.0 (12.0, 29.0)	51.0 (33.0, 72.8)
Ferritin, ng/ml	780.0 (404.2, 1405.0)	2491.5 (1266.0, 4751.0)
Missing	2338 (23.2)	115 (27.5)
C-reactive protein, mg/dl	11.0 (5.8, 18.5)	10.4 (5.0, 19.3)
Missing	2155 (21.4)	117 (27.9)
D-Dimer assay, ng/ml	462.0 (274.0, 989.5)	583.0 (392.0, 1090.0)
Missing	3703 (36.8)	174 (41.5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease; PVD, peripheral vascular disease.

<sup>a</sup>Missingness is shown if missing data are >2%.

Values are n (%) or median (interquartile range), unless otherwise indicated.

for baseline demographics and comorbid conditions, the odds of in-hospital death remained higher in the ESKD group compared to the non-ESKD group (adjusted OR 1.37, 95% CI 1.09–1.73; [Table 2](#)). Patient-level characteristics of those who achieved the primary outcome (expired or alive) are shown in [Supplementary Table S2](#).

Patients with ESKD had rates of mechanical ventilation similar to those for patients without ESKD (89 [21.2%] vs. 2076 [20.6%], respectively). In both the crude analysis and the adjusted analysis, the ESKD group did not have significantly higher odds of requiring mechanical ventilation than the non-ESKD group (OR 1.07, 95% CI 0.84–1.36 vs. adjusted OR 0.97, 95% CI 0.75–1.25).

The median length of hospital stay for patients discharged alive was higher in the ESKD group compared with the non-ESKD group (7.7 days [interquartile range {IQR} 4.8–13.4] vs. 6.1 days [IQR 3.4–10.8], respectively). In the crude analysis, the odds of having a length of stay of ≥7 days were higher in the ESKD group compared to the non-ESKD group (OR 1.62, 95% CI 1.27–2.06). After adjusting for baseline demographics and comorbid conditions, the adjusted OR was 1.57, 95% CI 1.22–2.02 ([Table 2](#)).

We studied various clinical characteristics as potential risk factors of in-hospital death among patients with ESKD and those without ESKD ([Tables 3 and 4](#); [Figure 2](#)).

For patients without ESKD, the independent risk factors for in-hospital death after adjusting for covariates in model 1 included increased age, male sex, cardiovascular disease, cancer, requiring mechanical ventilation, requiring vasoactive medications, high blood urea nitrogen level, low albumin level, high C-reactive protein level, and high log-transformed serum ferritin level. The diagnosis of hypertension and use of an ACE inhibitor or angiotensin II receptor blocker (ARB) were associated with a lower risk of in-hospital death ([Table 3](#)). After adjusting for variables in model 2, the

**Table 2 | Odds ratios for in-hospital outcomes among patients with and without end-stage kidney disease (the group without end-stage kidney disease is the reference)**

Outcomes	OR	95% CI	P
In-hospital death			
Unadjusted	1.38	1.12–1.70	0.003
Adjusted for baseline demographic <sup>a</sup>	1.47	1.17–1.83	<0.001
Adjusted for baseline demographic and comorbid conditions <sup>b</sup>	1.37	1.09–1.73	0.006
Mechanical ventilation			
Unadjusted	1.07	0.84–1.36	0.60
Adjusted for baseline demographic	1.08	0.84–1.38	0.56
Adjusted for baseline demographic and comorbid conditions	0.97	0.75–1.25	0.82
Length of stay (<7 vs. ≥7 d) <sup>c</sup>			
Unadjusted	1.62	1.27–2.06	<0.001
Adjusted for baseline demographic	1.61	1.27–2.06	<0.001
Adjusted for baseline demographic and comorbid conditions	1.57	1.22–2.02	<0.001

CI, confidence interval; OR, odds ratio.

<sup>a</sup>Basic demographic variables include age, sex, race/ethnicity.

<sup>b</sup>Comorbid conditions variables include body mass index, diabetes mellitus, hypertension, coronary artery disease, heart failure, peripheral vascular disease, asthma, chronic obstructive pulmonary disease, liver disease, and cancer.

<sup>c</sup>The analyses were performed only among those who were discharged alive.

independent risk factors for in-hospital death among patients without ESKD were increased age, male sex, DM, cardiovascular disease, cancer, requiring mechanical ventilation, and

requiring vasoactive medications (Table 3). Hypertension and use of ACE inhibitors or ARB were again associated with lower risk of in-hospital death.

**Table 3 | Univariate and multivariate logistic regression analyses of risk factors associated with in-hospital death in patients without ESKD**

Variables	Univariate			Multivariate (Model 1) <sup>d</sup>			Multivariate (Model 2) <sup>e</sup>		
	OR	95% CI	P	Adjusted OR	95% CI	P	Adjusted OR	95% CI	P
Age, yr	1.05	1.05–1.05	<0.001	<b>1.07</b>	1.07 – 1.08	<0.001	<b>1.08</b>	1.08 - 1.09	<0.001
Male	1.24	1.13–1.36	<0.001	<b>1.18</b>	1.03–1.35	0.02	<b>1.39</b>	1.23 - 1.58	<0.001
Race/ethnicity									
Non-Hispanic White	—	—	—	—	—	—	—	—	—
Non-Hispanic Black	0.71	0.62–0.80	<0.001	0.96	0.80–1.15	0.67	1.13	0.95 - 1.34	0.17
Hispanic	0.68	0.60–0.78	<0.001	0.95	0.79–1.14	0.55	0.94	0.79 - 1.12	0.52
Other	0.76	0.67–0.87	<0.001	1.04	0.86–1.26	0.68	0.98	0.81 - 1.17	0.79
Unknown	0.76	0.63–0.92	0.005	0.78	0.60–1.02	0.07	0.85	0.66 - 1.09	0.20
BMI, kg/m <sup>2</sup>									
18.5–29.9	—	—	—	—	—	—	—	—	—
<18.5	1.67	1.24–2.26	<0.001	0.95	0.64–1.40	0.79	1.20	0.83 - 1.72	0.34
≥30.0	0.78	0.71–0.87	<0.001	1.05	0.90–1.22	0.57	0.98	0.84 - 1.13	0.76
Diabetes mellitus	1.35	1.23–1.48	<0.001	1.06	0.93–1.22	0.39	<b>1.16</b>	1.02 - 1.32	0.02
Hypertension	1.60	1.46–1.76	<0.001	<b>0.80</b>	0.69–0.93	0.004	<b>0.845</b>	0.73 - 0.98	0.03
Use of ACE inhibitor/ARB	1.20	1.08–1.33	<0.001	<b>0.83</b>	0.72–0.97	0.02	<b>0.78</b>	0.67 - 0.90	<0.001
Cardiovascular disease <sup>a</sup>	2.24	2.02–2.49	<0.001	<b>1.32</b>	1.14 - 1.53	<0.001	<b>1.32</b>	1.14 - 1.52	<0.001
Respiratory disease <sup>b</sup>	1.08	0.95–1.23	0.24	—	—	—	—	—	—
Cancer	1.62	1.38–1.89	<0.001	<b>1.33</b>	1.09–1.63	0.006	<b>1.30</b>	1.07 - 1.57	0.009
Chronic liver disease	0.83	0.62–1.11	0.20	—	—	—	—	—	—
Mechanical ventilation	16.40	14.60 – 18.50	<0.001	<b>9.00</b>	6.48–12.47	<0.001	<b>7.42</b>	5.42 - 10.18	<0.001
Vasoactive medication <sup>c</sup>	16.55	14.71–18.61	<0.001	<b>3.96</b>	2.89–5.45	<0.001	<b>5.33</b>	3.92 - 7.24	<0.001
Hemoglobin, g/l	0.94	0.92–0.96	<0.001	0.98	0.95–1.01	0.23	—	—	—
WBC, 1000/μl	1.08	1.07–1.09	<0.001	—	—	—	—	—	—
Lymphocyte, 1000/μl	0.83	0.77–0.89	<0.001	0.93	0.86–1.01	0.07	—	—	—
Neutrophil, 1000/μl	1.10	1.09–1.11	<0.001	—	—	—	—	—	—
BUN, mg/dl	1.03	1.03–1.03	<0.001	<b>1.02</b>	1.01–1.02	<0.001	—	—	—
Albumin, g/l	0.45	0.42–0.49	<0.001	<b>0.76</b>	0.68–0.85	<0.001	—	—	—
CRP, mg/dl	1.05	1.05–1.06	<0.001	<b>1.03</b>	1.02–1.04	<0.001	—	—	—
Log serum ferritin, ng/ml	1.37	1.30–1.45	<0.001	<b>1.13</b>	1.04–1.23	0.004	—	—	—

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin ii receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; WBC, white blood count.

<sup>a</sup>Cardiovascular diseases include coronary artery disease, heart failure, and peripheral vascular disease.

<sup>b</sup>Respiratory diseases include asthma and chronic obstructive pulmonary disease.

<sup>c</sup>Vasoactive medications include inotropes and vasopressors.

<sup>d</sup>Model 1: Adjusted for age, sex, race/ethnicity, BMI, diabetes mellitus, hypertension, cardiovascular disease, cancer, mechanical ventilation, use of vasoactive medication, hemoglobin, lymphocyte, blood urea nitrogen, albumin, C-reactive protein, and ferritin.

<sup>e</sup>Model 2: Variables included in model 1, excluding laboratory values and inflammatory markers.

Bold data indicate xxx.

**Table 4 | Univariate and multivariate logistic regression analyses of risk factors associated with death among patients with ESKD**

Variable	Univariate			Multivariate (Model 1) <sup>d</sup>			Multivariate (Model 2) <sup>e</sup>		
	OR	95% CI	P	Adjusted OR	95% CI	P	Adjusted OR	95% CI	P
Age, yr	1.03	1.01–1.04	0.001	<b>1.05</b>	1.021–1.07	< 0.001	<b>1.05</b>	1.02–1.07	< 0.001
Male	1.51	0.97–2.33	0.07	0.91	0.50–1.66	0.77	1.12	0.65–1.94	0.68
Race/ethnicity									
Non-Hispanic White	—	—	—	—	—	—	—	—	—
Non-Hispanic Black	0.42	0.24–0.73	0.002	<b>0.47</b>	0.22–0.98	0.04	<b>0.48</b>	0.24–0.96	0.04
Hispanic	0.57	0.30–1.06	0.07	0.68	0.28–1.65	0.39	0.68	0.30–1.53	0.35
Other	1.12	0.60–2.12	0.72	1.62	0.65–4.04	0.98	1.48	0.66–3.32	0.34
Unknown	0.53	0.18–1.62	0.27	0.56	0.11–2.73	0.69	0.55	0.13–2.34	0.42
BMI, kg/m <sup>2</sup>									
18.5–29.9	—	—	—	—	—	—	—	—	—
<18.5	1.02	0.40–2.64	0.96	1.01	0.29–3.50	0.98	1.07	0.35–3.25	0.92
≥30.0	1.01	0.63–1.61	0.97	1.15	0.58–2.29	0.69	0.95	0.51–1.79	0.88
Diabetes	0.87	0.57–1.33	0.53	0.90	0.49–1.33	0.74	0.98	0.56–1.72	0.94
Hypertension	0.75	0.36–1.56	0.45	0.73	0.26–2.00	0.53	0.62	0.25–1.51	0.29
Use of ACE inhibitor/ARB	0.72	0.43–1.21	0.22	0.76	0.37–1.54	0.44	0.82	0.41–1.61	0.56
Cardiovascular disease <sup>a</sup>	1.28	0.85–1.94	0.24	1.32	0.74–2.37	0.34	1.07	0.63–1.81	0.81
Respiratory disease <sup>b</sup>									
Cancer	1.64	0.81–3.32	0.17	1.96	0.74–1.15	0.17	1.77	0.72–4.34	0.21
Chronic liver disease	1.27	0.45–3.56	0.65	—	—	—	—	—	—
Mechanical ventilation	14.66	8.1526.35	<0.001	<b>13.45</b>	4.34–41.65	<0.001	<b>10.44</b>	3.62–30.19	<0.001
Vasoactive medication <sup>c</sup>	12.42	7.10–21.75	<0.001	2.09	0.68–6.40	0.20	<b>2.93</b>	1.06–8.09	0.04
Hemoglobin, g/l	1.02	0.92–1.15	0.64	1.15	0.97–1.37	0.10	—	—	—
WBC, 1000/μl	1.06	1.01–1.11	0.01	—	—	—	—	—	—
Lymphocyte, 1000/μl	0.61	0.39–0.94	0.03	<b>0.60</b>	0.41–0.90	0.01	—	—	—
Neutrophil, 1000/μl	1.09	1.04–1.16	0.001	—	—	—	—	—	—
BUN, mg/dl	1.01	1.00–1.01	0.03	<b>1.01</b>	1.00–1.03	0.005	—	—	—
Albumin, g/l	0.57	0.42–0.79	<0.001	0.64	0.39–1.04	0.07	—	—	—
CRP, mg/dl	1.04	1.02–1.06	<0.001	1.02	0.98–1.01	0.29	—	—	—
Log serum ferritin, ng/ml	1.69	1.31–2.19	<0.001	<b>1.47</b>	1.03–2.11	0.04	—	—	—

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin ii receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; WBC, white blood count.

<sup>a</sup>Cardiovascular diseases include coronary artery disease, heart failure and peripheral vascular disease.

<sup>b</sup>Respiratory diseases include asthma and chronic obstructive pulmonary disease.

<sup>c</sup>Vasoactive medications include inotropes and vasopressors.

<sup>d</sup>Model 1: adjusted for age, sex, race/ethnicity, BMI, diabetes mellitus, hypertension, cardiovascular disease, cancer, mechanical ventilation, use of vasoactive medication, hemoglobin, lymphocyte, blood urea nitrogen, albumin, C-reactive protein and ferritin.

<sup>e</sup>Model 2: Variables included in model 1, excluding all the laboratory values and inflammatory markers.

Bold data indicate xxx.

Among patients with ESKD, independent risk factors for in-hospital death after adjustment in model 1 were increased age, requiring mechanical ventilation and lymphopenia, elevated blood urea nitrogen level, and high log-transformed serum ferritin level. In model 2, the independent risk factors for in-hospital death were increased age, requiring mechanical ventilation, and vasoactive medication use. Black race was associated with a significantly lower risk of death among patients with ESKD in both models (OR 0.47, 95% CI 0.22–0.98 and OR 0.48, 95% CI 0.24–0.96, in models 1 and 2, respectively; [Table 4](#) and [Figure 2](#)).

In a comparison of the odds of in-hospital death in the ESKD group versus the non-ESKD group, sensitivity analysis incorporating the assumption that those who were still hospitalized either all experienced death or were all discharged alive did not significantly alter the results ([Supplementary Table S3](#)). Similarly, sensitivity analyses examining risk factors for mortality in the ESKD and non-ESKD cohorts separately did not substantially alter the results

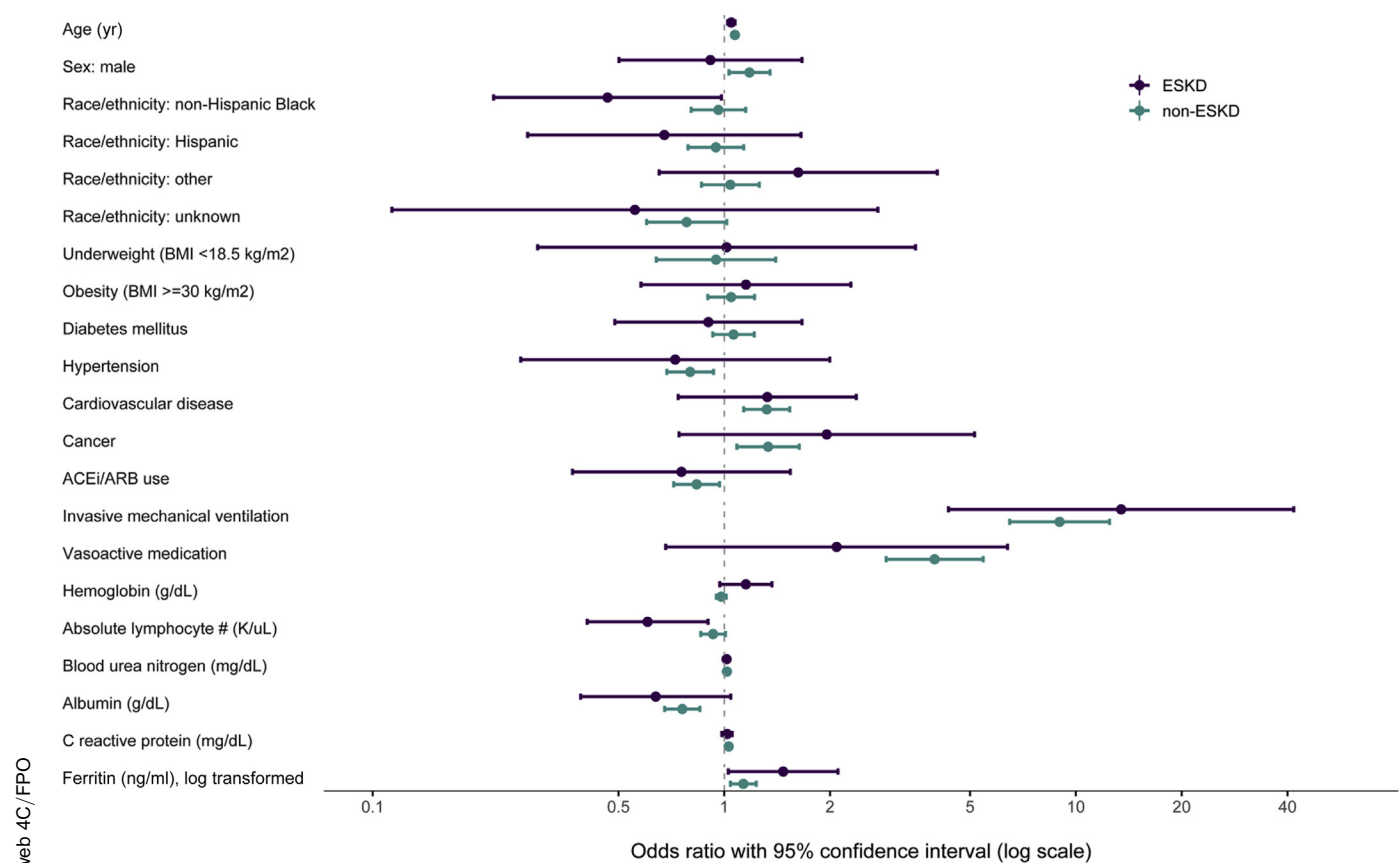
([Supplementary Tables S4](#) and [S5](#)). [Supplementary Table S6](#) shows the odds ratios of in-hospital death of patients with and without ESKD, stratified by mechanical ventilation.

## DISCUSSION

We examined the clinical characteristics, outcomes, and risk factors for death in patients with ESKD on chronic dialysis infected with COVID-19. The primary finding was that the risk for in-hospital death was significantly increased among patients with ESKD compared to the non-dialysis population. The increased mortality risk persisted after adjustment for patient demographics and comorbid conditions. Among prespecified secondary outcomes, patients with ESKD had a significantly longer length of hospital stay. In contrast, there was no significant difference between patients with versus without ESKD in the need for mechanical ventilation.

Patients on dialysis have long been known to have a greatly increased risk of death compared to the general population. For patients starting hemodialysis, the expected 5-year





**Figure 2 | Forest plot showing the risk factors of in-hospital death, by end-stage kidney disease (ESKD) status.** Reference levels for the variables assessed: sex, female; race/ethnicity, non-Hispanic White; weight, normal/overweight (body mass index [BMI], 18.5–29.9 kg/m<sup>2</sup>). ACE-i, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker.

survival rate is only 42% in the United States,<sup>13</sup> a risk similar to that of various forms of cancer.<sup>26</sup> Although the reason for increased risk of death among patients with ESKD has not been fully elucidated, it can be at least partially understood through the greater accumulated comorbidities in this population. The rates of DM, heart disease, vascular disease, and other conditions are substantially greater than they are in the non-dialysis population.<sup>27</sup> Because of this difference, our finding of a significantly increased risk of in-hospital mortality among ESKD patients with COVID-19 compared to non-dialysis patients would appear to be intuitive. However, adjusting for comorbidities did not meaningfully change the greater risk observed in the ESKD cohort. This finding suggests that other unmeasured characteristics of the ESKD patients accounted for the increased risk, which may be related to host response to infection.

Patients with ESKD have an increased risk for infections and infection-related mortality. The increased risk of infections is likely related to a dysregulated immune system, as the uremic milieu has been associated with disturbances in both innate as well as adaptive immunity. Alterations in the function of neutrophils, Natural Killer cells, macrophages, and T and B lymphocytes, along with inflammation induced

by the dialysis procedure itself, lead to impaired host immunity.<sup>28,29</sup> Infections are the second most common cause of death for patients on dialysis, with some studies finding a several-hundred-fold higher annual mortality rate secondary to sepsis as compared to that in the general population.<sup>11</sup> The aforementioned susceptibility to both viral and bacterial infections is highly relevant to consider regarding mortality outcomes in patients with ESKD who are infected with SARS-CoV-2.

We found that among the 419 patients with ESKD hospitalized with COVID-19 infection, 133 died (31.7%). Previous studies have examined mortality risk in smaller patient cohorts.<sup>25</sup> Preprint data from Wuhan University reported 37 COVID-19–positive HD patients, of which 6 (16.2%) died.<sup>15</sup> Another preprint report from Wuhan by Li *et al.*<sup>30</sup> reported on 66 patients with confirmed infection and 24 cases with suspected COVID-19. The proportion of patients who died was 13.3% (12 of 90 with confirmed or suspected infection). In Spain, Goicoechea *et al.* reported on a study of 36 HD patients with COVID-19 infection, 11 (30.6%) of whom had died.<sup>23</sup> The Brescia Renal COVID Task Force in Italy reported 24 (42.1%) deaths among 57 HD patients.<sup>24</sup> Our results are similar to those from the European centers and from recent

single-center US data.<sup>25</sup> This may be consistent with the findings that patients with COVID-19 infection from China have generally been reported as having better outcomes by a variety of different metrics.

In our study, we found that independent risk factors for death among patients with ESKD were largely similar to those for patients without ESKD. A notable difference that defies obvious explanation was that HTN and the use of ACE inhibitors or ARBs were significant protective factors against death among patients without ESKD. Several articles have proposed the protective effect of renin-angiotensin-aldosterone system inhibitors on lung injury and cardiac injury in COVID-19 disease, although the subject has remained unsettled.<sup>18,31</sup> Given that patients with HTN are often prescribed these inhibitors, one could postulate that the inhibitors could be providing a protective effect among those with HTN. Yet after adjusting for use of ACE inhibitors or ARBs, the protective effect of HTN for in-hospital death persisted. In a recent paper from the United Kingdom, the OpenSAFELY Collaborative also found a protective effect of HTN.<sup>10</sup> In their *post hoc* analysis, the authors found a significant interaction between HTN and age, whereby HTN was associated with lower mortality only among those aged  $\geq 70$  years. The reason for this finding is unclear. The diagnosis of HTN is common in the older population, which may reflect continual access to medical care.

Within the ESKD group, we found that Black race was associated with a significantly reduced risk of death. In contrast, previous studies have found that Black race increases the risk of dying from COVID-19.<sup>32</sup> Our finding of protection associated with Black race among ESKD patients with COVID-19 defies easy explanation. Notably, Black patients with ESKD generally have better survival while on dialysis compared to White patients. This inherent survival advantage may partly explain our finding of improved hospital survival of Black ESKD patients with COVID-19.<sup>33–35</sup> Dialysis dosing, nutritional factors with higher BMI as a protective mechanism, and racial differences in inflammatory responses are some possible hypotheses that may confer the racial difference in survival improved dialysis survival.<sup>34</sup> Any racial differences in inflammatory or coagulation parameters could be highly relevant in COVID-19 disease. More recently, evidence has suggested the role of the apolipoprotein L1 (APOL1) gene allele in the difference in mortality between Black patients with ESKD compared to their White counterparts. Several studies have found that although APOL1 was strongly associated with the development of ESKD, there was no significant association with cardiovascular diseases.<sup>36–38</sup> It may be that this is why among Blacks, the rate of ESKD exceeded the rate of mortality and cardiovascular deaths,<sup>39–41</sup> which may help explain the reduced mortality we observed during COVID-19 infection.

Inflammatory markers, including serum ferritin, have been associated with the severity of COVID-19.<sup>42,43</sup> In our study, we found that within the ESKD group, serum ferritin levels were higher in patients who died compared to those

who were alive (3644.0 ng/ml [IQR 1753.0, 7687.0] vs. 2138.0 ng/ml [IQR 1142.0, 3969.0], respectively). Additionally, we found that serum ferritin level was an independent risk factor for in-hospital death for both the non-ESKD and ESKD groups (Tables 3 and 4). In one study, a serum ferritin increase of  $>200\%$  was found to be a potentially useful screening marker for dialysis patients infected with COVID-19.<sup>44</sup> Serum ferritin level potentially could be used in future research as a screening tool for severity of COVID-19 in ESKD patients.

To date, this is by far the largest cohort of hospitalized patients with COVID-19 comparing mortality between patients with versus without ESKD in a diverse patient population. In order to increase the validity of the data, we had prespecified operational definitions for exposures, covariates, and outcomes, as well as rigorous adjudication by 2 independent reviewers for ESKD exposure. Additionally, the findings of the study are further strengthened by various analytical approaches and sensitivity analyses to minimize confounding biases.

The limitations of the study include the retrospective observational design, which leaves open the possibility of missing variables that potentially could be important explanatory factors. As BMI was a risk factor associated with in-hospital death in other studies,<sup>45,46</sup> our study was limited by 10% of missing BMI data. We had, however, attempted to handle the missing BMI data through multiple imputation. In addition, despite the larger size of this study compared to other reports, the ESKD sample may still have been relatively underpowered to find other statistically significant risk factors in mortality. Another limitation is the inability to adjust for remdesivir and dexamethasone, the only 2 drugs associated with improved outcomes for COVID-19.<sup>47,48</sup> As the evidence for these 2 drugs came after the surge of COVID-19 cases in our health system, only a small proportion of patients received these 2 drugs. Only 51 patients (0.5%) in the non-ESKD group received remdesivir, and none of the patients in the ESKD group received it. Fewer than 3% of patients in both groups received dexamethasone (Supplementary Table S1).

In conclusion, we found that among hospitalized patients with COVID-19, mortality risk was increased in patients with ESKD as compared to that in the general population. Remarkably, we found that among patients with ESKD who were of Black race, there was a significantly lower risk of death from COVID-19. Taken altogether, the results suggest both a need for further research and the continued need for careful scrutiny and infection control procedures in the ESKD population at risk for COVID-19.

## METHODS

### Study design and cohort

This was a retrospective observational cohort study of a large New York health system. Data for this study were obtained from the 13 hospitals using the enterprise inpatient electronic health record Sunrise Clinical Manager (Allscripts, Chicago, IL). All adult

(age  $\geq 18$  years) patients who tested positive by polymerase chain reaction testing of a nasopharyngeal sample for COVID-19 and were hospitalized from March 1, 2020, to April 27, 2020, were eligible. The patients were followed up through May 27, 2020. For patients who had multiple qualifying hospital admissions, we included only the first hospitalization. Patients were excluded if they were transferred out of the health system or were admitted to an inpatient obstetric service. The Institutional Review Board of Northwell Health approved the study protocol before the commencement of the study.

### Data cleaning and preparation process

Prior to analysis, we carried out a data-cleaning process to screen for duplicate records and missing data and performed range checks to assess for outliers and erroneous data. We excluded outliers and duplicate records.

### ESKD exposure

Primary exposure was prehospitalization diagnosis of ESKD with dialysis dependence. ESKD diagnosis was defined using International Classification of Diseases, Tenth Revision code N18.6. Two study investigators (VS and JSH) performed independent adjudication of the ESKD diagnosis through manual chart review of hospital admission and nephrology consultation notes for the following key search terms: “ESRD,” “ESKD,” “end stage renal,” and “end stage kidney.” We cross-checked ESKD diagnosis by evaluating inpatient HD and peritoneal dialysis orders. Those identified as ESKD without inpatient dialysis orders underwent further manual chart review.

In order to avoid misclassification of non-dialysis-dependent kidney transplant recipients into the exposed group, we performed additional verification. Kidney transplant was defined using International Classification of Diseases, Tenth Revision codes T86.1, T86.10, T86.11, T86.12, T86.13, T86.19, and Z94.0 and adjudication through manual chart review using the following key search terms: “kidney transplant,” “renal transplant,” “kidney txp,” “renal txp,” “DDRT” (deceased donor renal transplant), “LRRT” (living related renal transplant), “LURT” (living unrelated renal transplant), and “LDT” (living donor transplant). Adjudication for the kidney transplant diagnosis was carried out by members of the Nephrology COVID-19 Consortium.

### Outcomes

The primary outcome was in-hospital death. The secondary outcomes were mechanical ventilation and hospital length of stay.

### Variables assessed

We collected data on patient demographics, baseline history of comorbid conditions, home medications, dialysis-specific data elements, and details on hospital admissions. Comorbid conditions and home medications were determined from provider-entered past medical history and admission medication reconciliation. Dialysis modality and dialysis vascular access were determined from inpatient dialysis order entry. We collected details of hospital admission such as ICU stay, mechanical ventilation, vasopressor support, and baseline laboratory test results within 48 hours of hospital admission. Due to the COVID-19 pandemic, many additional ICUs were created in nontraditional hospital areas and units. Hence, ICU stay was defined as either one of the following: need for invasive mechanical ventilation, need for vasopressor or inotrope support, being under the care of an ICU service, or being in a known ICU location.

### Statistical analysis

We computed descriptive statistics including means and standard deviations for normally distributed continuous measures, medians and IQRs for skewed continuous measures, and proportions for categorical measures. We used Fisher’s exact test to compare categorical variables, and nonparametric Kruskal-Wallis tests for continuous variables.

To determine if ESKD diagnosis was associated with in-hospital outcomes of death (primary outcome), mechanical ventilation or length of stay of  $\geq 7$  days (secondary outcomes), we performed univariate and multivariate logistic regression for each outcome separately. In a stepwise fashion, we adjusted for demographics, including age, sex, and race/ethnicity, and then adjusted for demographics as well as comorbid conditions including DM, HTN, cardiovascular diseases (coronary artery disease, heart failure, and peripheral vascular disease), respiratory diseases (asthma and chronic obstructive pulmonary disease), chronic liver disease, and cancer.

For the primary outcome (in-hospital death), we performed several predefined sensitivity analyses to determine the robustness of our results. In the primary analysis, we restricted the analysis to patients who died or were discharged alive. In a sensitivity analysis, we included patients still hospitalized in the logistic regression to compare the risk of death of patients with versus without ESKD (174 patients [1.7% of cohort]). We repeated the regression model by assuming all those still hospitalized to have experienced death, and another model by assuming all those still hospitalized to have been discharged alive.

We conducted stratified analyses to investigate the risk factors of death in the subgroups of ESKD and non-ESKD separately, with the hypothesis that the risk factors of death and the magnitude of risk factors would differ between the 2 groups. In the absence of COVID-19 disease, low hemoglobin levels, low serum albumin levels, and high blood urea nitrogen levels were shown to be risk factors of death among those with ESKD,<sup>49,50</sup> but they were not typical risk factors of death for those without ESKD. In each ESKD and non-ESKD subgroup, we performed two distinct logistic regression models. The variables selected were decided *a priori*, and chosen based upon known risk factors for mortality in the general population and for patients with ESKD.<sup>51–55</sup> For model 1, we included the following variables: age, sex, race/ethnicity, BMI, DM, HTN, use of ACE inhibitors or ARB, cardiovascular disease (coronary artery disease, heart failure, or peripheral vascular disease), cancer, mechanical ventilation, use of vasoactive medications (vasopressors or inotropes), hemoglobin, absolute lymphocyte count, serum blood urea nitrogen level, serum albumin level, serum C-reactive protein level, and serum ferritin level. BMI was included as a categorical variable, with 3 groups representing underweight (BMI  $< 18.5$  kg/m<sup>2</sup>), normal weight (BMI between 18.5 and 29.9 kg/m<sup>2</sup>), and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>). Serum ferritin levels were log transformed in order to normalize distribution, and the log-transformed values were used in the models. Model 2 included variables similar to those in model 1, but laboratory test values were removed. The variables in model 2 are recognized as important risk factors of in-hospital death, including clinical characteristics at time of admission and characteristics of illness severity (mechanical ventilation and vasoactive medications).

### Missing data

To account for missing data in the regression models, we performed multiple imputation for chained equations using predictive mean

matching with 50 imputations and 20 iterations (mice R package, version 3.9.0).<sup>56</sup> Model 1 and 2 estimates and standard errors were calculated using Rubin's rules.<sup>57</sup> The variables used for the multiple imputation procedure are described in the [Supplementary Methods](#). D-dimer data were missing to a substantial degree, with 37% missing data in the non-ESKD group and 42% missing data in the ESKD group; thus, we did not perform multiple imputation for this variable nor include it in any of the models. Other than for D-dimer, we performed multiple imputation for all the missing data including BMI, ACE-inhibitor/ARB use, basic laboratory tests, and the inflammatory markers C-reactive protein and ferritin.

All statistical tests were 2-sided, and  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). This study followed the EQUATOR Reporting Guidelines—REporting of studies Conducted using Observational Routinely-collected health Data (RECORD).<sup>58</sup>

## APPENDIX

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## DISCLOSURE

KDJ serves as a consultant for Astex Pharmaceuticals and Natera. All the other authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary Methods.](#)

**Table S1.** In-hospital medications of patients with and without end-stage kidney disease.

**Table S2.** Characteristics of patients, by alive or expired status (the still-admitted group is not shown).

**Table S3.** Sensitivity analyses of odds ratios for in-hospital death among patients with and without ESKD, including all patients who were still admitted (non-ESKD group is the reference).

**Table S4.** Sensitivity analyses of multivariate logistic regression (Model 1‡) of risk factors associated with in-hospital death in patients without ESKD, including all patients who were still admitted.

**Table S5.** Sensitivity analysis of multivariate logistic regression (Model 1‡) of risk factors associated with in-hospital death in patients with ESKD, including all patients who were still admitted.

**Table S6.** Odds ratios for in-hospital outcomes among patients with and without end-stage kidney disease, stratified by mechanical ventilation status (non-ESKD group is the reference).

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