Acute and Chronic Dialysis during the Coronavirus Disease 2019 (COVID-19) Pandemic

A thesis submitted by

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Abstract

Throughout the coronavirus disease 2019 (COVID-19) pandemic, patients receiving dialysis have been particularly vulnerable to poor outcomes, and in the work presented here, we have sought to characterize their epidemiology at each phase. Among critically ill patients with COVID-19 who initiated dialysis for acute kidney injury, greater baseline kidney function and greater urine output at the time of dialysis initiation were associated with kidney recovery. During this early phase of the pandemic (spring and early summer of 2020), patients receiving chronic dialysis were found to be at high risk of developing COVID-19, and among those with COVID-19, 90-day mortality approached 25%. As the pandemic evolved, testing became more widely available, thus increasing diagnosis of mild and asymptomatic cases, and infection control measures were widely implemented in healthcare facilities. During this phase of the pandemic (fall and early winter of 2020), in-center dialysis did not have greater association with COVID-19 than home dialysis, once residence in a long-term care facility was adjusted for. Lastly, vaccines against severe acute respiratory syndrome coronavirus 2 became available in December 2021. Patients receiving chronic dialysis were found to have a robust initial seroresponse; however, this was observed to wane over time, suggesting that additional vaccine doses may be appropriate for this vulnerable population.

Dedication

To the healthcare workers of the world, who have given so much of themselves

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List of Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ADL	Activities of daily living
AKI	Acute kidney injury
AKI-KRT	Acute kidney injury treated with kidney replacement therapy
ARB	Angiotensin receptor blocker
CDC	Centers for Disease Control and Prevention
CHF	Congestive heart failure
CKRT	Continuous kidney replacement therapy
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
DCI	Dialysis Clinic, Inc.
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ICU	Intensive care unit
KRT	Kidney replacement therapy
LTCF	Long-term care facility
PVD	Peripheral vascular disease
REDCap	Research Electronic Data Capture (REDCap)
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCr	Serum creatinine
SOFA	Sequential Organ Failure Assessment
STOP-COVID	Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19

Chapter 1: Introduction

As of March 2022, the coronavirus disease 2019 (COVID-19) pandemic has claimed 6 million lives worldwide.[1] It has caused unprecedented societal and economic upheaval around the globe.[2,3] Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), its presentation can range from asymptomatic, incidental diagnosis to critical illness with multiorgan failure.[4]

COVID-19 began as a cluster of respiratory illnesses in Wuhan, China in December of 2019. It soon spread to the rest of the world, with the first case arriving in the United States in January 2020,[5] and community spread likely occurring in the United States by February.[6] Due to the virus's high transmission rate, this stage of the pandemic was concentrated in densely populated urban areas.[7] Hospitals in major cities, particularly in New York City, were stretched to capacity in space, equipment, and personnel.[8] At this time, mild illness due to COVID-19 was likely underdiagnosed, due to a combination of underrecognition of the symptoms and limited testing supplies.[9] Acute kidney injury occurred in 17 to 46% of hospitalized patients, with higher risk associated with more severe illness.[10–13] Given the concurrently high case fatality rates at this time,[14,15] it became particularly meaningful to investigate the prognosis of acute kidney injury in critically ill patients with COVID-19.

In addition, patients receiving maintenance dialysis were hypothesized to be particularly vulnerable to poor outcomes. The vast majority of dialysis patients are obligated to congregate three times a week for life-sustaining medical care, a critical risk factor at a time when physical distancing was emphasized as a precaution against contracting

SARS-CoV-2.[16] Patients may have uremia-associated immunocompromise and/or high comorbid burden.[17–20] Indeed, morbidity and mortality due to COVID-19 were high among residents of long-term care facilities, due to their close proximity and overall frailty.[21–23] It therefore became important to characterize the epidemiology of COVID-19 among patients receiving chronic dialysis.

By the fall of 2020, COVID-19 had spread from urban areas to the rest of the country.[24,25] Testing was more widely available, enabling diagnosis of more mild cases.[26] As dialysis clinics implemented infection control measures, such as masking and physical distancing, attention among dialysis physicians turned to the patients receiving home dialysis, who tend to be somewhat less frail than their in-center counterparts.[27] We thus sought to characterize the epidemiology of COVID-19 among patients receiving home dialysis.

In December 2020, the first vaccines against SARS-CoV-2 received approval by the Food and Drug Administration, and, as rollout began in earnest, the pandemic entered a new phase. Vaccines were highly effective at preventing COVID-19 among healthy adults, and effectiveness against death or severe illness requiring hospitalization approached 100%.[28–30] However, further study was needed to characterize the response to vaccines among patients receiving maintenance dialysis. Of note, patients receiving maintenance dialysis often have suboptimal response to other vaccines and require additional or higher doses.[17,31] Accordingly, there was a need to assess both the strength and the durability of the vaccine-generated response.

Thus, each phase of the COVID-19 pandemic has presented unique challenges to the dialysis community, and we have sought to close this knowledge gap at each stage. We first identified predictors of kidney recovery and mortality among critically ill patients with COVID-19-associated acute kidney injury. We then characterized the epidemiology of COVID-19 (1) during the first surge in spring 2020 among all patients receiving maintenance dialysis and (2) during the latter half of 2020 among patients receiving home dialysis as compared to in-center dialysis. Lastly, we assessed the seroresponse to SARS-CoV-2 vaccination over six months among patients receiving maintenance dialysis.

Chapter 2: Kidney Recovery and Death in Critically Ill Patients with COVID-19-associated Acute Kidney Injury Treated with Dialysis: the STOP-COVID Cohort[32]

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[32] Hsu CM, Gupta S, Tighiouart H, et al. Kidney Recovery and Death in Critically Ill Patients With COVID-19-Associated Acute Kidney Injury Treated With Dialysis: The STOP-COVID Cohort Study. *Am J Kidney Dis*. 2022;79(3):404-416.e1. doi:10.1053/j.ajkd.2021.11.004

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2.1 Introduction

Acute kidney injury (AKI) occurs frequently in patients with coronavirus disease 2019 (COVID-19), affecting 17 to 46% of hospitalized patients, 14% to 20% of whom are treated with kidney replacement therapy (KRT).[10–13] Dialysis is resource-intensive, and long-term dialysis impacts patients' quality of life and other clinically important outcomes.[33–35] Furthermore, studies have demonstrated high mortality among critically ill patients with COVID-19 whose AKI is treated with dialysis.[10,36] Accurate prognostication of both long-term dialysis dependence and mortality therefore has key implications for clinical outcomes and quality of life, and may affect decision-making in the setting of critical illness and AKI.

At this time, no widely accepted tools exist for prognostication of kidney recovery from AKI and in particular from AKI treated by KRT (AKI-KRT). Historically, mortality as a competing outcome has been difficult to account for.[37,38] Studies of kidney recovery have been further limited by variation in recovery patterns and lack of detailed data on clinical status at the time of AKI or of KRT initiation.[37–39] In comparison, AKI associated with COVID-19, though occurring via multiple possible mechanisms,[40] has less heterogeneity with respect to timing and underlying cause; thus, a pattern for recovery may be discernable.

Using detailed clinical data from a large multicenter cohort of critically ill patients with COVID-19, we first investigated the association of AKI severity with kidney function at the time of hospital discharge. Next, among patients with AKI-KRT, we examined the clinical factors which may predict kidney recovery, using baseline characteristics and measures of clinical status at the time of dialysis initiation.

2.2 Methods

2.2.1 Study design and data collection

We used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), a multicenter cohort study that enrolled consecutive adults (≥18 years old) with laboratory-confirmed COVID-19 admitted to participating intensive care units (ICUs) at 68 hospitals across the United States. We included patients admitted to ICUs between March 1 and June 22, 2020. This study was approved by the institutional review boards at all participating sites with a waiver of informed consent. All data except dates were deidentified.

Study personnel at each site collected data by detailed chart review using a standardized electronic case report form via a secure Research Electronic Data Capture (REDCap) database. Patient-level data included baseline information on demographics, coexisting conditions, symptoms, medications before hospital admission, and vital signs on ICU admission; daily data for the 14 days after ICU admission on physiologic and laboratory values, medications, nonmedication treatments, and organ support; and outcomes data on discharge and death, including kidney function at discharge. Additional details regarding the STOP-COVID parent study are reported elsewhere.[36,41]

2.2.2 AKI severity and outcomes in the ICU cohort

Initial analyses evaluated the entire STOP-COVID population, excluding those receiving dialysis at hospital admission, those without outcome data, those still hospitalized at last follow-up, those without kidney function assessment at discharge, and those without a baseline serum creatinine concentration (Scr); these patients composed the ICU cohort. These descriptive analyses examined kidney outcomes and mortality by severity of AKI. Baseline serum creatinine (SCr) was defined as the lowest of three values: 1) lowest preadmission SCr value between 7 and 365 days prior to admission; 2) SCr on hospital admission; and 3) SCr on ICU Day 1. AKI severity was determined by calculating the ratio of the peak SCr in the first 14 days after ICU admission relative to the baseline value, using thresholds defined by KDIGO AKI staging.[42] Similarly, among survivors, the ratio of the discharge SCr to the baseline, as well as ongoing treatment with dialysis at discharge was used to categorize kidney recovery. Mortality was defined by vital status at hospital discharge. Outcomes were compared by AKI severity.

2.2.3 Kidney outcomes and mortality in the AKI-KRT subcohort

2.2.3.1 Patient population and exposures

Further analysis focused on the subset of patients who received dialysis during the first 14 days after ICU admission, termed the AKI-KRT subcohort. KRT Day 1 was defined as a patient’s first day of dialysis.

Exposures of interest identified *a priori* based on clinical importance and availability in the dataset were demographics (age, sex, race, ethnicity), baseline medical status (history of diabetes mellitus, estimated glomerular filtration rate [eGFR] at baseline using the CKD-EPI equation with a race coefficient),[43] initial mode of dialysis (continuous kidney replacement therapy [CKRT], intermittent hemodialysis, or peritoneal dialysis), markers of illness severity on KRT Day 1 (serum albumin, arterial pH, 24-hour urine output, maximum number of vasopressors or inotropes received that day), and occurrence of a major cardiac event (ventricular tachycardia, ventricular fibrillation, or cardiac arrest) on or preceding KRT Day 1.

2.2.3.2. Outcomes

Patients were followed until either hospital discharge or death. Kidney recovery was defined as independence from dialysis at discharge. The date of recovery was the date of last dialysis; if it could not be determined (because daily data on KRT were only collected for the first 14 days after ICU admission and on hospital discharge), it was set as the date of discharge (see Item S1 for details). Among survivors discharged with recovery, SCr at the time of discharge was used to calculate discharge eGFR, which was then compared to baseline eGFR in a series of descriptive analyses.

2.2.3.3. Statistical analysis

Several regression methods were used to assess predictors of recovery while accounting for hospital mortality. These regression analyses were applied to the same group of patients, the AKI-KRT subcohort, to assess for consistency in results. Missing exposure variables were imputed using methods described in the Item S1.

Primary analyses used multinomial logistic regression to associate covariates of interest with the outcome of kidney recovery, using kidney nonrecovery as the reference outcome and death as an alternate outcome.

Two secondary analyses were conducted. First, ordinal logistic regression analysis was performed to associate covariates with the composite outcome of kidney nonrecovery or death and with the outcome of death alone, thus treating death as the least desirable outcome, followed by kidney nonrecovery with kidney recovery as the most desirable outcome. Second, because logistic regression does not account for differences in follow-up time, instead assuming the same follow-up time for all patients, we used cause-specific time-to-recovery analysis to assess the instantaneous rate of recovery, treating death as a competing event. (Time-to-recovery was not used for primary analysis due to uncertainty around the date of recovery, with most patients' recovery status being reported only at hospital discharge.) Those who were discharged without kidney recovery were censored at the time of discharge.

For each of these 3 approaches, 3 sets of analyses were conducted: (1) primary analyses utilized all *a priori* specified exposure variables; (2) parsimonious analyses included only demographic characteristics and baseline medical status assessments; and (3) expanded analyses further incorporated medications received on or prior to KRT Day 1 (corticosteroids, tocilizumab, and remdesivir, chosen for clinical relevance) and additional assessments of clinical status on KRT Day 1 (use of mechanical ventilation, the coagulation component of the SOFA [Sequential Organ Failure Assessment] score, and the liver component of the SOFA score).

Statistical analyses were performed with SAS EG v7.14 (SAS Institute, Cary, NC).

2.3 Results

2.3.1 AKI severity and outcomes in the ICU cohort

Among 5154 patients enrolled in STOP-COVID, 741 had incomplete data reporting, and 192 were receiving maintenance dialysis at admission; therefore, 4221 patients constituted the ICU cohort (Figure 2.1). Of these, 2681 (63%) were male, and the mean age was 61 ± 15 [SD] years; 1085 (26%) had baseline eGFR ≤ 60 mL/min/1.73m^2 (Table 2.1).

Figure 2.1. Flow diagram of the study population.

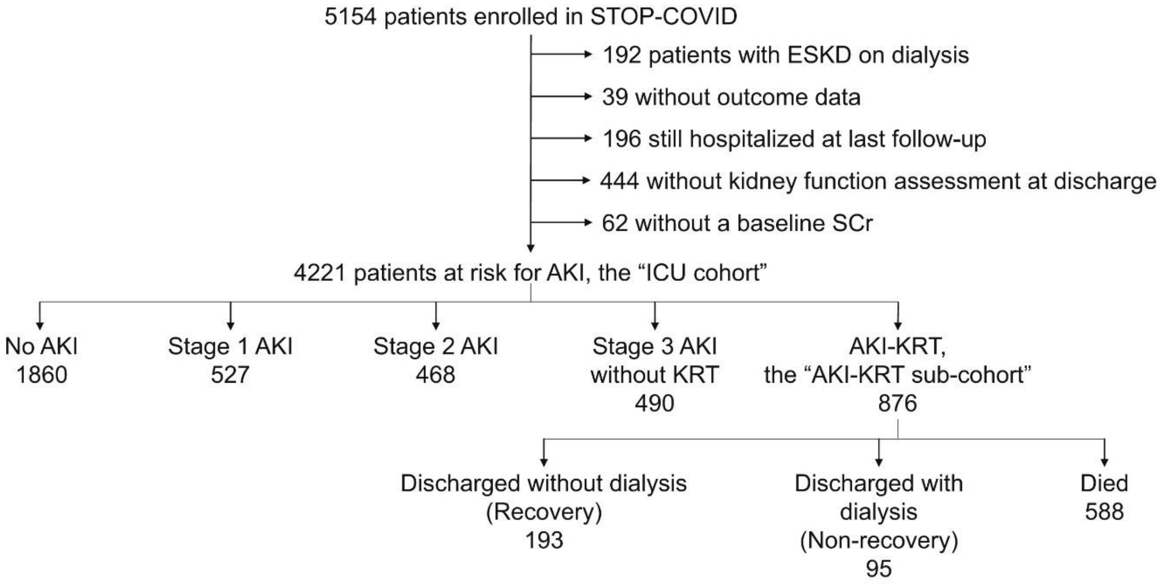


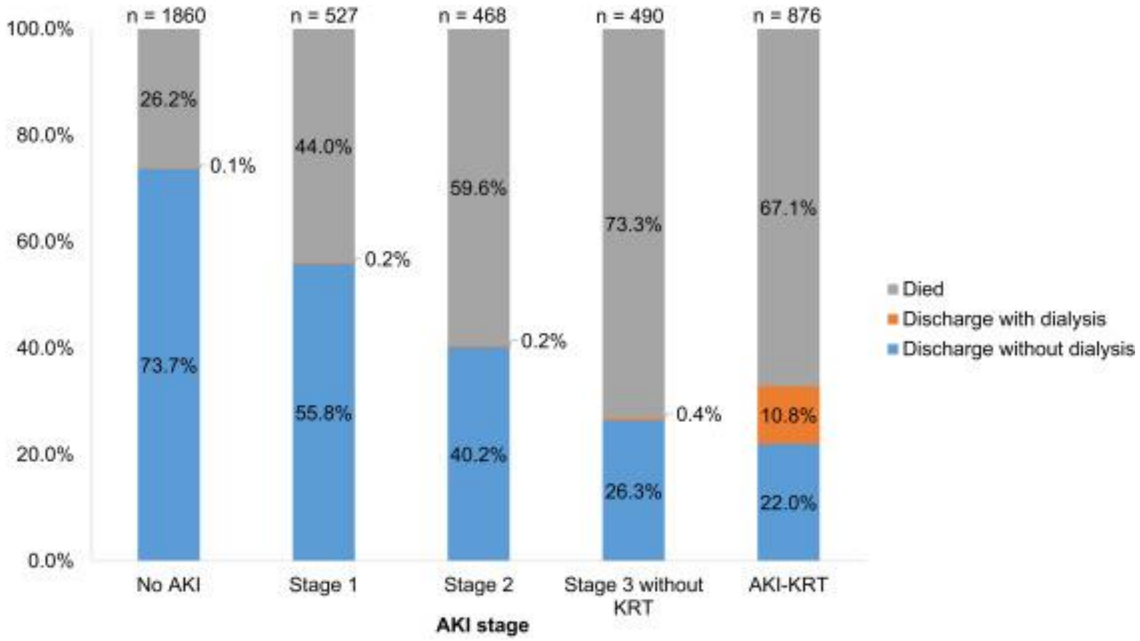
Table 2.1. Characteristics of STOP-COVID population at risk for AKI, stratified by baseline eGFR (mL/min/1.73m^2)

	Overall	**eGFR > 60**	**eGFR 31-60**	**eGFR 16-30**	**eGFR ≤15**
N, %	4221	3136 (74%)	777 (18%)	217 (5%)	91 (2%)
Age	61 ± 15	59 ± 15	69 ± 12	68 ± 14	64 ± 15
Male	2681 (63.5)	2007 (64.0)	498 (64.1)	121 (55.8)	55 (60.4)
Race					
White	1625 (38.5)	1220 (38.9)	305 (39.3)	67 (30.9)	33 (36.3)
Black or African-American	1242 (29.4)	848 (27.0)	268 (34.5)	89 (41.0)	37 (40.7)
Asian	244 (5.8)	186 (5.9)	44 (5.7)	12 (5.5)	2 (2.2)
American Indian / Alaska Native	23 (0.5)	18 (0.6)	5 (0.6)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	27 (0.6)	17 (0.5)	7 (0.9)	2 (0.9)	1 (1.1)
More than one race	44 (1.0)	37 (1.2)	5 (0.6)	1 (0.5)	1 (1.1)
Unknown / Not reported	1016 (24.1)	810 (25.8)	143 (18.4)	46 (21.2)	17 (18.7)
Ethnicity					
Hispanic or Latino	1025 (24.3)	850 (27.1)	128 (16.5)	33 (15.2)	14 (15.4)
Not Hispanic or Latino	2671 (63.3)	1884 (60.1)	567 (73.0)	156 (71.9)	64 (70.3)
Unknown	525 (12.4)	402 (12.8)	82 (10.6)	28 (12.9)	13 (14.3)
Diabetes mellitus	1756 (41.6)	1176 (37.5)	400 (51.5)	130 (59.9)	50 (54.9)
Serum albumin on ICU day 1 (g/dL)	3.20 [2.80, 3.60]	3.20 [2.80, 3.60]	3.20 [2.80, 3.60]	3.00 [2.50, 3.40]	3.00 [2.60, 3.50]
Arterial pH on ICU day 1	7.37 [7.30, 7.43]	7.39 [7.31, 7.44]	7.34 [7.28, 7.41]	7.30 [7.21, 7.39]	7.27 [7.21, 7.35]
UOP on ICU day 1 (mL/day)					
500+	1448 (34.3)	1104 (35.2)	260 (33.5)	63 (29.0)	21 (23.1)
50-499	678 (16.1)	448 (14.3)	152 (19.6)	59 (27.2)	19 (20.9)
<50	91 (2.2)	53 (1.7)	15 (1.9)	7 (3.2)	16 (17.6)
Unknown	2004 (47.5)	1531 (48.8)	350 (45.0)	88 (40.6)	35 (38.5)
Number of vasopressors/inotropes needed on ICU day 1					
0	2568 (60.8)	1978 (63.1)	429 (55.2)	120 (55.3)	41 (45.1)
1	1216 (28.8)	892 (28.4)	228 (29.3)	60 (27.6)	36 (39.6)
≥2	437 (10.4)	266 (8.5)	120 (15.4)	37 (17.1)	14 (15.4)
Major cardiac event on ICU day 1	119 (2.8)	70 (2.2)	32 (4.1)	11 (5.1)	6 (6.6)
Medications administered on ICU day 1					
Corticosteroids	634 (15.0)	455 (14.5)	124 (16.0)	41 (18.9)	14 (15.4)
Tocilizumab	227 (5.4)	172 (5.5)	43 (5.5)	10 (4.6)	2 (2.2)
Remdesivir	130 (3.1)	115 (3.7)	13 (1.7)	2 (0.9)	0 (0.0)
Mechanical ventilation on ICU day 1	2500 (59.2)	1798 (57.3)	493 (63.4)	141 (65.0)	68 (74.7)
Platelets on ICU day 1 (x10^3/μL)					
150+	3242 (76.8)	2454 (78.3)	560 (72.1)	162 (74.7)	66 (72.5)
100-149	553 (13.1)	376 (12.0)	137 (17.6)	28 (12.9)	12 (13.2)
<100	204 (4.8)	138 (4.4)	42 (5.4)	16 (7.4)	8 (8.8)
Unknown	222 (5.3)	168 (5.4)	38 (4.9)	11 (5.1)	5 (5.5)
Bilirubin on ICU day 1 (mg/dL)					
<1.2	3081 (73.0)	2275 (72.5)	576 (74.1)	161 (74.2)	69 (75.8)
1.2-1.9	280 (6.6)	214 (6.8)	54 (6.9)	8 (3.7)	4 (4.4)
2.0+	120 (2.8)	87 (2.8)	19 (2.4)	10 (4.6)	4 (4.4)
Unknown	740 (17.5)	560 (17.9)	128 (16.5)	38 (17.5)	14 (15.4)

Age is displayed as mean ± SD. Serum albumin and arterial pH are displayed as median [IQR]. All other data are displayed as frequency (%). eGFR, estimated glomerular filtration rate; ICU, intensive care unit; UOP, urine output

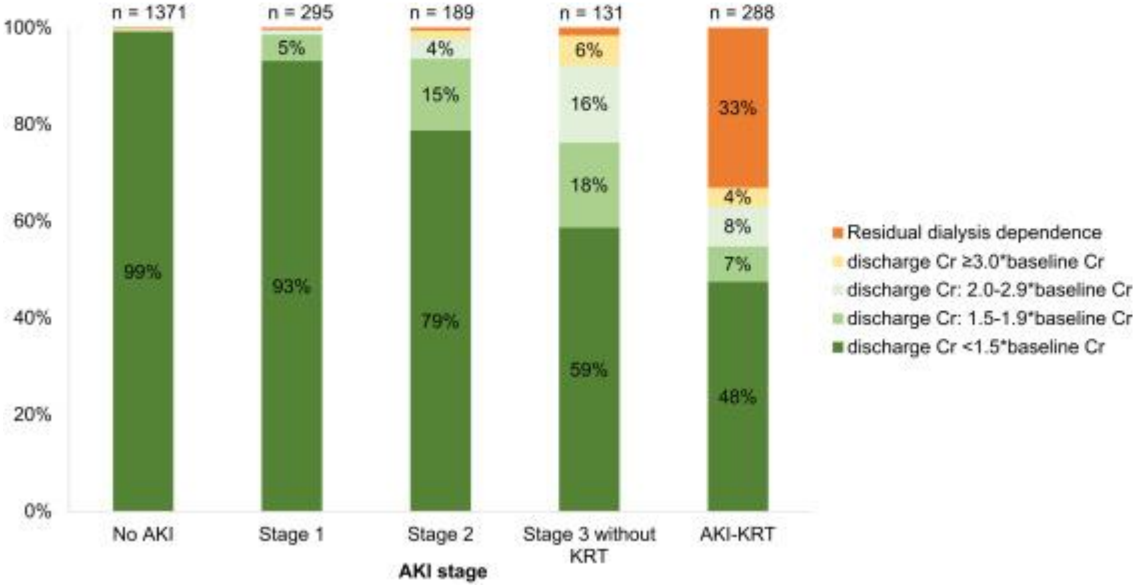
Within the first 14 days after ICU admission, 2361 patients (56%) developed AKI, including 527 (12%) with stage 1, 468 (11%) with stage 2, 490 (12%) with stage 3 without KRT, and 876 (21%) who received KRT (Figure 2.1). More severe AKI was associated with greater mortality; among those with no AKI, AKI stage 1, AKI stage 2, AKI stage 3 without KRT, and AKI-KRT, 26%, 44%, 60%, 73%, and 67% died, respectively (Figure 2.2). Of those with AKI-KRT, 11% were discharged while continuing to receive dialysis. Discharge with dialysis occurred in less than 0.5% of patients with other stages of AKI; since, in this study, AKI stage was defined by its peak severity within the first 14 days of ICU admission, these patients must have received KRT beginning after the first 14 days of ICU admission. Among survivors, more severe AKI was associated with higher likelihood of kidney nonrecovery at discharge as well as higher SCr at discharge. Among those with no AKI, AKI stage 1, AKI stage 2, AKI stage 3 without KRT, and AKI-KRT, 1%, 7%, 11%, 41%, and 52% had a discharge SCr ≥1.5 times their baseline SCr or were continuing to receive KRT at discharge (Figure 2.3).

Figure 2.2. Outcomes of the ICU cohort



AKI stage 1 defined as peak Scr is 1.5-1.9 times baseline Scr; AKI stage 2, peak Scr is 2.0-2.9 times baseline; AKI stage 3 without KRT, peak Scr is ≥3.0 times baseline.

Figure 2.3. Kidney outcomes of the ICU cohort, survivors only.



AKI stage 1 defined as peak serum Cr is 1.5-1.9 times baseline serum Cr; AKI stage 2, peak serum Cr is 2.0-2.9 times baseline; AKI stage 3 without KRT, peak serum Cr is ≥3.0 times baseline. For clarity, bars less than 4% are unlabeled.

2.3.2 Kidney outcomes and mortality in the AKI-KRT subcohort

Among the 876 patients with AKI-KRT, mean age was 61 ± 12 [SD] years, 626 (71.5%) were male, 362 (41.3%) were Black, and 177 (20.2%) were Hispanic or Latino. A minority (362 [41%]) had baseline eGFR ≤60 mL/min/1.73m^2. Continuous kidney replacement therapy (CKRT) was the most common initial mode of therapy (n=590 [67.4%]), and most patients (n=665 [75.9%]) required at least one vasopressor/inotrope on the day of KRT initiation. Urine output was less than 500 mL/d in 521 patients (59.5%) and was less than 50 mL/d in 149 patients (17.0%) on KRT day 1. Median serum albumin was 2.5 [IQR: 2.1-2.8] g/dL and median arterial pH was 7.27 [IQR 7.21-7.34]. Before KRT initiation, 287 patients (32.8%) had received steroids, 155 (17.7%) received tocilizumab, and 54 (6.2%) received remdesivir. The median time elapsed from ICU admission to KRT day 1 was 3 [IQR: 1-6] days (Table 2.2).

Table 2.2. Characteristics of the AKI-KRT population, stratified by baseline eGFR (mL/min/1.73m^2)

	Overall	eGFR > 60	eGFR 31-60	eGFR 16-30	eGFR ≤15
Number, %	**876 (100%)**	**514 (59%)**	**210 (24%)**	**89 (10%)**	**63 (7%)**
Age	61 ± 12	59 ± 12	64 ± 12	63 ± 11	61 ± 15
Male sex	626 (71.5)	385 (74.9)	151 (71.9)	51 (57.3)	39 (61.9)
Race					
White	269 (30.7)	156 (30.4)	67 (31.9)	23 (25.8)	23 (36.5)
Black or African-American	362 (41.3)	192 (37.4)	100 (47.6)	43 (48.3)	27 (42.9)
Asian	33 (3.8)	23 (4.5)	8 (3.8)	2 (2.2)	0 (0.0)
American Indian/Alaska Native	7 (0.8)	4 (0.8)	3 (1.4)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	7 (0.8)	5 (1.0)	0 (0.0)	1 (1.1)	1 (1.6)
More than one race	8 (0.9)	7 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)
Unknown / Not reported	190 (21.7)	127 (24.7)	31 (14.8)	20 (22.5)	12 (19.0)
Ethnicity					
Hispanic or Latino	177 (20.2)	131 (25.5)	24 (11.4)	13 (14.6)	9 (14.3)
Not Hispanic or Latino	596 (68.0)	321 (62.5)	164 (78.1)	63 (70.8)	48 (76.2)
Unknown	103 (11.8)	62 (12.1)	22 (10.5)	13 (14.6)	6 (9.5)
Diabetes mellitus	471 (53.8)	248 (48.2)	127 (60.5)	61 (68.5)	35 (55.6)
Initial mode of KRT					
CKRT 24h/day	471 (53.8)	278 (54.1)	115 (54.8)	48 (53.9)	30 (47.6)
CKRT 12h/day or less	119 (13.6)	72 (14.0)	32 (15.2)	9 (10.1)	6 (9.5)
Intermittent hemodialysis	270 (30.8)	150 (29.2)	62 (29.5)	31 (34.8)	27 (42.9)
Peritoneal Dialysis	8 (0.9)	7 (1.4)	0 (0.0)	1 (1.1)	0 (0.0)
Unknown	8 (0.9)	7 (1.4)	1 (0.5)	0 (0.0)	0 (0.0)
Serum albumin on KRT day 1 (g/dL)	2.5 [2.1, 2.8]	2.49 [2.10, 2.80]	2.5 [2.10, 2.90]	2.4 [2.0, 2.7]	2.6 [2.2, 3.1]
Arterial pH on KRT day 1	7.27 [7.21, 7.34]	7.27 [7.21, 7.33]	7.27 [7.20, 7.33]	7.28 [7.23, 7.34]	7.28 [7.21, 7.36]
UOP on KRT day 1 (mL/day)					
500+	266 (30.4)	154 (30.0)	71 (33.8)	25 (28.1)	16 (25.4)
50-499	372 (42.5)	229 (44.6)	88 (41.9)	35 (39.3)	20 (31.7)
<50	149 (17.0)	87 (16.9)	29 (13.8)	19 (21.3)	14 (22.2)
Unknown	89 (10.2)	44 (8.6)	22 (10.5)	10 (11.2)	13 (20.6)
Number of vasopressors/inotropes needed on KRT day 1					
0	211 (24.1)	119 (23.2)	48 (22.9)	25 (28.1)	19 (30.2)
1	400 (45.7)	233 (45.3)	96 (45.7)	39 (43.8)	32 (50.8)
≥2	265 (30.3)	162 (31.5)	66 (31.4)	25 (28.1)	12 (19.0)
Major cardiac event prior to or on KRT day 1	55 (6.3)	37 (7.2)	10 (4.8)	5 (5.6)	3 (4.8)
Medications administered on or prior to KRT day 1					
Corticosteroids	287 (32.8)	169 (32.9)	82 (39.0)	20 (22.5)	16 (25.4)
Tocilizumab	155 (17.7)	99 (19.3)	40 (19.0)	10 (11.2)	6 (9.5)
Remdesivir	54 (6.2)	41 (8.0)	11 (5.2)	2 (2.2)	0 (0.0)
Mechanical ventilation on KRT day 1	840 (95.9)	502 (97.7)	202 (96.2)	77 (86.5)	59 (93.7)
Platelets on KRT day 1 (x10^3/μL)					
150+	703 (80.3)	415 (80.7)	174 (82.9)	65 (73.0)	49 (77.8)
100-149	106 (12.1)	62 (12.1)	23 (11.0)	15 (16.9)	6 (9.5)
<100	61 (7.0)	36 (7.0)	12 (5.7)	7 (7.9)	6 (9.5)
Unknown	6 (0.7)	1 (0.2)	1 (0.5)	2 (2.2)	2 (3.2)
Bilirubin on KRT day 1 (mg/dL)					
<1.2	594 (67.8)	317 (61.7)	153 (72.9)	72 (80.9)	52 (82.5)
1.2-1.9	124 (14.2)	95 (18.5)	24 (11.4)	2 (2.2)	3 (4.8)
2.0+	89 (10.2)	66 (12.8)	14 (6.7)	5 (5.6)	4 (6.3)
Unknown	69 (7.9)	36 (7.0)	19 (9.0)	10 (11.2)	4 (6.3)
Days from ICU admission to KRT day 1	3 [1, 6]	4 [2, 7]	3.5 [2, 6]	2 [1, 4]	1[0, 2]

Age is displayed as mean ± SD. Serum albumin, arterial pH, and days from ICU admission to KRT day 1 are displayed as median [IQR]. All other data are displayed as frequency (%).

2.3.2.1 Discharge status

Of the 876 patients with AKI-KRT, 588 (67%) died, 95 (11%) were discharged alive and were continuing to receive dialysis at discharge, and 193 (22%) had kidney recovery by the time of discharge. In multinomial logistic regression models, lower baseline kidney function and lower urine output on KRT day 1 were each associated with kidney nonrecovery (Figure 2.4). The odds of nonrecovery approximately doubled with each more severe baseline eGFR category, with odds ratios of 2.09 (95% CI, 1.09-4.04), 4.27 (95% CI, 1.99-9.17), and 8.69 (95% CI, 3.07-24.55) for patients with eGFR of 31-60, 16-30, ≤15 mL/min/1.73m^2, respectively, compared to patients with eGFR >60 mL/min/1.73m^2. Compared to patients with urine output ≥500 mL/d, oliguria (urine output 50-499 mL/d) was associated with a 2.10-fold increased odds of nonrecovery (95% CI, 1.14-3.88) and anuria (urine output <50mL/d) was associated with a 4.02-fold increased odds of nonrecovery (95% CI, 1.72-9.39) (Figure 2.4, Table S2.1). A descriptive analysis of survivors also showed the association of both lower baseline eGFR and lower urine output with kidney nonrecovery (Figure 2.5). Of note, those who died had much shorter follow-up time (median 7 [IQR: 3-15] days) compared to those who either had kidney recovery (31 [23-44] days) or kidney nonrecovery (30 [21-42.5]), limiting interpretation of predictors of mortality.

Results were similar in secondary analyses utilizing ordinal logistic regression: Older age, baseline eGFR ≤15 mL/min/1.73m^2, lower arterial pH, and lower urine output were each associated with the composite outcome of nonrecovery or death, and older age, non-Black race, initiation with non-CKRT modality, lower albumin, lower arterial pH, anuria,

Figure 2.4. Multivariable multinomial regression, using recovery as the reference outcome.

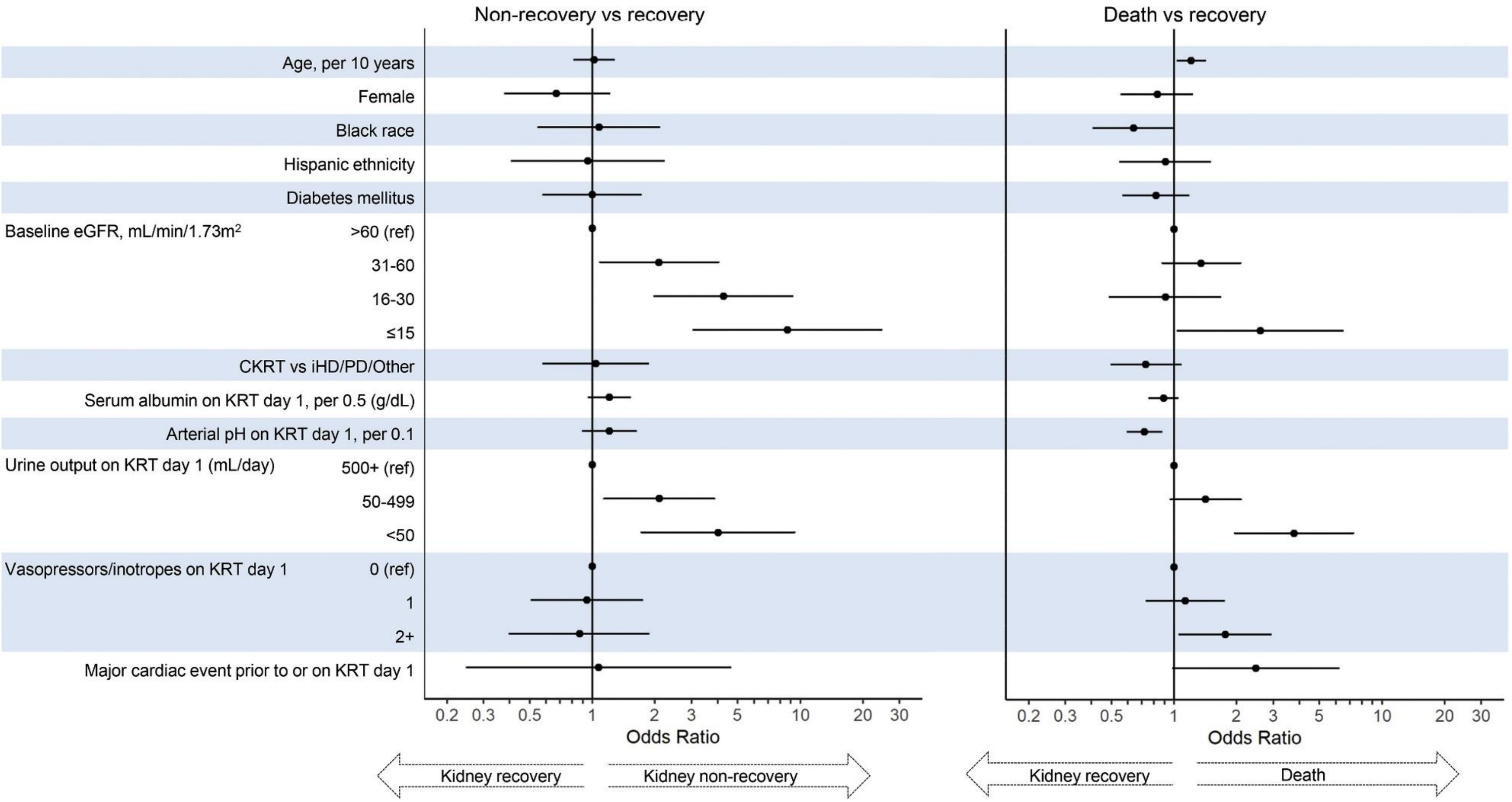
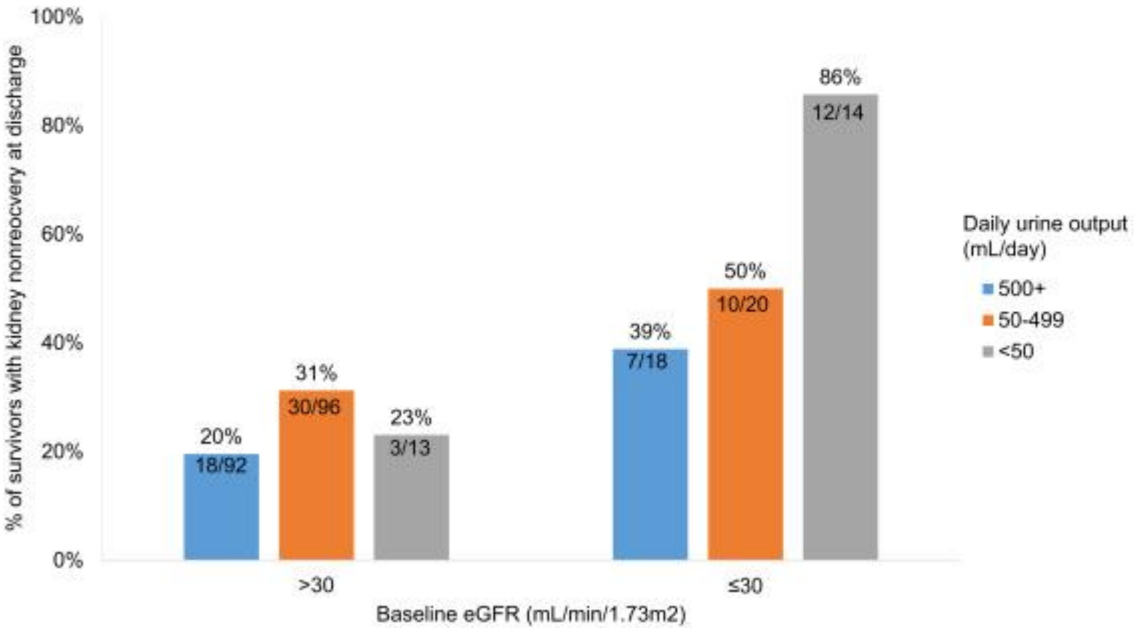


Figure 2.5. Percent of survivors with kidney nonrecovery at discharge, by baseline eGFR and urine output on KRT day 1.



Each bar shows the percent with kidney nonrecovery at discharge, out of the survivors. For example, 92 patients with a baseline eGFR > 30 mL/min/1.73 m^2 and urine output of ≥500 mL/d on KRT day 1 survived to discharge; 18 (20%) of these patients had kidney nonrecovery at discharge.

need for two or more vasopressors/inotropes, and a preceding major cardiac event were each associated with mortality alone (Table S2.2). The cause-specific time-to-recovery analysis that treated death as a competing event identified Black race, baseline eGFR >15 mL/min/1.73m^2, and greater urine output as associated with a higher likelihood of recovery (Table S2.3). Parsimonious and expanded analyses did not yield notably different results, though effect sizes were somewhat increased in parsimonious models (Tables S2.1-S2.3).

2.3.2.2 Kidney function at discharge among survivors

Among the 288 patients with AKI-KRT who survived to discharge, 162 (56.2%), 64 (22%), 40(14%), and 22 (8%) had initial eGFR of greater than 60, 31-60, 16-30, and ≤15 mL/min/1.73m^2 respectively. At discharge, 95 patients (33%) were continuing to receive dialysis. Lower baseline eGFR and oligoanuria (urine output <500 mL/d) on the day of KRT initiation were each associated with a higher likelihood of nonrecovery (Figure 2.6). Individuals with higher baseline GFR were more likely to have recovery of kidney function to an eGFR of ≥60 mL/min/1.73m^2 at discharge (Figure 2.7).

Figure 2.6. Outcome of kidney nonrecovery (vs recovery) at hospital discharge, among survivors

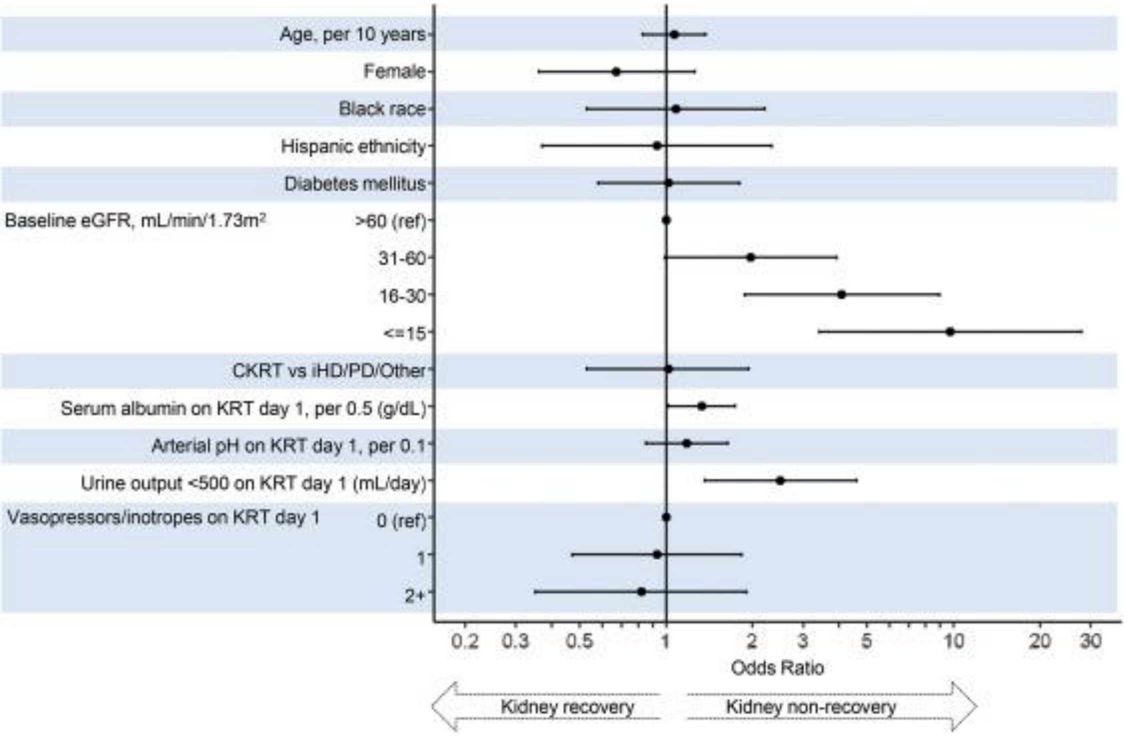
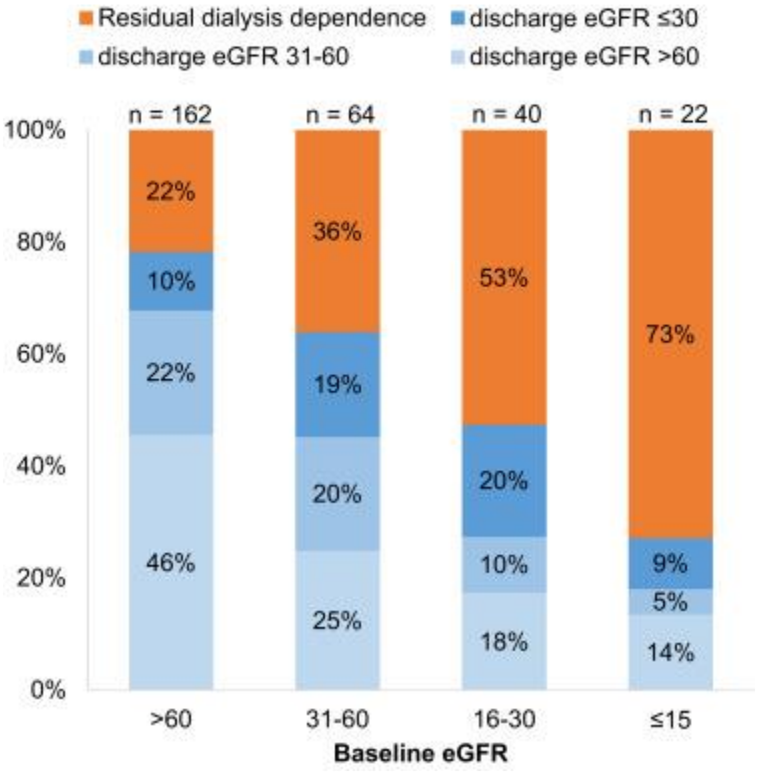


Figure 2.7. Kidney function at discharge among AKI-KRT patients, survivors only



2.4 Discussion

In this multicenter cohort study of 4221 critically ill patients with COVID-19 admitted to ICUs at 68 US hospitals, we identified several noteworthy findings regarding outcomes in patients with AKI. First, greater AKI severity was associated with higher in-hospital mortality and, among survivors, worse kidney function at discharge. Second, among patients who had AKI and were treated with KRT, almost two-thirds died. Of those who survived to discharge, approximately two-thirds recovered kidney function and were not continuing to receive dialysis at discharge. Third, across multiple analyses, lower baseline eGFR and oligoanuria at dialysis initiation were each associated with lower likelihood of recovery from AKI-KRT.

Detailed study of kidney recovery among patients with COVID-19 with AKI-KRT has been limited. A single-center study in New York City from approximately the same time period as the current report found that, of 347 patients hospitalized with COVID-19 who developed AKI-KRT, only 87 (25%) survived to discharge;[10] among those who survived, 70% were not continuing to receive dialysis at discharge, findings that are comparable to our results. A small study in Berlin, Germany from the same time period reported the outcomes of 74 patients with COVID-19 admitted to an ICU who developed AKI-KRT.[44] Compared to our study, fewer patients had decreased eGFR at baseline, which may account for their higher rate of recovery, with only 3 of 34 survivors (8%) continuing to receive KRT at the end of follow-up. An earlier STOP-COVID study of patients enrolled through April 11, 2020, had found similar rates of in-hospital mortality and ongoing treatment with dialysis at discharge.

None of these studies have reported factors predictive of recovery from AKI-KRT. Our study expands on these data with a substantially larger cohort across multiple sites during the earliest wave of COVID-19 in the US. The results of this report also expand on prior studies conducted with the STOP-COVID cohort by investigating associations of clinical factors at the time of dialysis initiation with kidney outcomes, including kidney recovery.[36]

Since this study was conducted, COVID-19 management has evolved to include the greater use of corticosteroids and other immunomodulatory agents (e.g. tocilizumab) in patients with severe illness, as these agents have been demonstrated to have a beneficial effect on patient survival.[45,46] By contrast, our results showed steroids to be associated with greater mortality, perhaps indicating that, during this phase, they were selectively administered to those with more severe illness (Supplemental Table S2.1). Interestingly, the same analysis suggested an association between steroid use and kidney recovery, though it did not reach statistical significance; in a separate recent study, steroid use was associated with reduced risk for AKI progression.[47] The observed association of steroid use with better kidney outcomes should be more systematically explored in subsequent larger clinical/epidemiologic investigations. Tocilizumab and remdesivir, which are also both now used more widely than during the study period, were not significantly associated with either kidney or mortality outcomes in this study.

Compared to prior studies of AKI-KRT among critically ill patients without COVID-19, this study and other studies of patients with COVID-19 have found higher rates of in-hospital mortality and of ongoing treatment with dialysis at hospital discharge.[10,36,47–56] These differences in outcomes may reflect the profound multiorgan failure associated with COVID-19 during the initial spring 2020 surge. The higher rate of kidney nonrecovery may also be due to direct infection of the kidneys by the SARS-CoV-2 virus, though this remains controversial.[57–59] Moreover, many of the studies of AKI among patients with COVID-19, including this study, have been conducted in academic hospitals, which tend to experience a higher acuity of disease. Nevertheless, despite variation in the rates of each outcome in the present study as compared with prior research in non-COVID-19 settings, the predictors of kidney recovery identified in the current study were similar to those found in studies among critically ill patients without COVID-19.

The association of both lower baseline eGFR and oliguria at the time of KRT initiation with a lower likelihood of kidney recovery highlights that kidney recovery after AKI is dependent on both the preinjury level of kidney function as well as the severity of the injury itself. Both elements of this conceptual model have been noted in other studies of recovery from AKI. Multiple studies have associated lower kidney function before an AKI episode with a higher likelihood of ongoing dialysis treatment or subsequent CKD progression.[53,56,60,61] Of note, most of these studies were conducted in hospitalized patients without either a specified mechanism of AKI or a unifying underlying diagnosis, unlike this study that included only COVID-19 patients admitted to an ICU. Direct comparison of effect sizes is limited, however, by variation in outcome assessments. Other clinical predictors of kidney recovery have not been studied extensively. A prior prospective cohort study of ICU patients with AKI-KRT similarly noted an association between oliguria and ongoing treatment with dialysis, with kidney recovery assessed at 1 year.[53]

This work has considerable implications for clinical care, both during and following the COVID-19 pandemic. The magnitude of the effect sizes found in our models is striking. One may consider an example of comparing a patient with more than 500 mL/d of urine output at the time of dialysis initiation with a patient with anuria (less than 50 mL/d). Based on our findings, the odds of survival for the patient with normal urine output are

2.3 times higher than those of the patient with anuria, and his/her odds of kidney recovery are more than 4-fold increased. Compared with a patient with both anuria and eGFR of $\leq$15 mL/min/1.73m^2, a patient with neither condition has a 1.9-fold greater odds of survival and an almost 13-fold greater odds of kidney recovery. That a baseline eGFR $\leq$15 mL/min/1.73m^2 appears to confer some survival benefit may reflect earlier ICU admission and dialysis initiation for less severe illness in these patients with advanced CKD.

Accurate prognostication of outcomes can assist clinical decision-making when dialysis initiation is being considered for AKI. While nephrologists often use a "wait and see" approach in such cases; however, given the magnitude of effect sizes of factors such as reduced baseline eGFR and oliguria, one may reasonably assess the calculated odds and incorporate likelihood of kidney recovery and overall survival into conversations around goals of care. The Renal Physicians Association recommends shared decision-making in weighing the options of dialysis initiation, a time-limited trial of dialysis, or transition to end-of-life care.[6263] Given the high in-hospital mortality of patients with AKI-KRT and the impact of maintenance dialysis on quality of life, such conversations are critical to providing care consistent with patients' goals and values.

This study has several strengths, particularly the detailed data collected by manual chart review in a large multicenter cohort of patients admitted to 68 ICUs around the United States, including acute severity of illness metrics obtained on the day of dialysis initiation. Although there is a heterogeneity of baseline burden of comorbid conditions, including baseline kidney function, an additional strength is a unifying nonsurgical, primary cause of acute illness—in this case COVID-19—with a clear temporal pattern, thus reducing the heterogeneity present in many AKI-KRT studies. While AKI due to COVID-19 may occur by multiple pathogenic mechanisms,[40] it may be interesting to examine how well baseline eGFR and oliguria predict outcomes in other medical AKI populations.

We also acknowledge several limitations. First, SCr and KRT data were only collected for the first 14 days following ICU admission and on hospital discharge, and as a result, outcomes were most reliably assessed at discharge. Logistic regression analysis was chosen to reflect this outcome assessment, but it assumes similar follow-up time among patients. Therefore, associations of exposures with mortality may have been biased by less follow-up time, though, given the overall short follow-up time for all patients, this bias is likely minimal, and similar results in time-to-event sensitivity analysis are reassuring. In addition, the uncertain timing of kidney recovery in some patients creates a bias toward the null in the time-to-recovery analysis. Furthermore, lack of post-discharge follow-up data precluded analysis of kidney recovery occurring after discharge, thus potentially underestimating kidney recovery rates. Reasons for KRT initiation were not captured. We were unable to determine how many deaths occurred after transfer to conservative management, which may partially account for the greater mortality rate observed among those with AKI stage 3 without KRT than those with AKI-KRT. Finally, addressing death as a competing outcome is always a challenge in studies of AKI-KRT outcomes, and the high mortality rate in this dataset likewise limits conclusions.

In summary, in this large cohort study of critically ill patients with COVID-19, decreased eGFR and oliguria at the time of dialysis initiation were each significantly associated with a lower likelihood of kidney recovery. The magnitude of the associations presented here may assist prognostication of long-term dialysis treatment, which carries implications for patients' physical health and quality of life.

Chapter 3: COVID-19 Among US Dialysis Patients: Risk Factors and Outcomes From a National Dialysis Provider[64]

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[64] Hsu CM, Weiner DE, Aweh G, et al. COVID-19 Among US Dialysis Patients: Risk Factors and Outcomes From a National Dialysis Provider. *Am J Kidney Dis*. 2021;77(5):748-756.e1. doi:10.1053/j.ajkd.2021.01.003

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3.1 Introduction

Patients with kidney failure who receive maintenance dialysis are particularly vulnerable to coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The average age of those receiving maintenance dialysis patients is 65 years old and these patients typically have multiple medical comorbid conditions, including diabetes, obesity, and uremia-induced impaired immunity, all of which increase their risk for poor outcomes should they develop COVID-19.[14,15,17–19,65] As a more socioeconomically disadvantaged group than the general population, including residence in more densely populated urban areas, they are at higher risk of acquiring SARS-CoV-2.[66,67] Additionally, most dialysis patients cannot practice effective physical distancing due to the need for in-center hemodialysis and associated transportation, as well as frequent reliance on social support and caregivers for assistance with daily activities or medication management. Confluence of these factors potentiates risk in the many who reside in long-term care facilities.[16,68–70]

Studies in China, Italy, the United Kingdom, and the United States (New York and southern California) show that maintenance dialysis patients with COVID-19 experience higher mortality and more severe disease compared to the general population.[71–77] As of 2017, approximately 524,000 patients in the United States were receiving dialysis, constituting a large at-risk population.[69] By June of 2020, the Centers for Medicare & Medicaid Services reported a COVID-19 prevalence of 3.8% in the dialysis population,[78] but further characterization is needed. Given the lack of national, generalizable data on COVID-19 in the vulnerable maintenance dialysis population, we characterized risk factors for COVID-19 among dialysis patients treated by a medium-sized, national dialysis organization. Additionally, among those diagnosed with COVID-19, we characterized risk of and risk factors for death.

3.2 Methods

Dialysis Clinic Inc. (DCI) is a national not-for-profit dialysis provider caring for more than 15,000 maintenance dialysis patients at 260 outpatient dialysis clinics in 29 states. All dialysis patients with the diagnosis of COVID-19 in DCI clinics between February 17, 2020 and June 1, 2020 were included in this retrospective cohort study, with outcomes ascertained through August 31, 2020. This initial 15-week period reflects the early surge of COVID-19 in the United States. We sought to describe our outpatient dialysis provider experience and determine risk factors for COVID-19 as well as for all-cause death within 90 days of a COVID-19 diagnosis. To mitigate bias from geographic imbalance of COVID-19 spread, in this analysis we only included patients from clinics with at least one case diagnosed with COVID-19. All patients in each of these clinics were included, but patients being treated with dialysis for acute kidney injury were excluded.

Based on contemporary practices, SARS-CoV-2 infection status was assessed via nasopharyngeal or oropharyngeal swabs sent locally for reverse transcriptase polymerase chain reaction (RT-PCR) testing that was approved by the FDA under Emergency Use Authorization or, if unavailable locally, through the DCI Labs contracted vendor beginning in April 2020 (using either the Hologic Panther Fusion or Cobas SARS-CoV-2

Assay [Roche Diagnostics]). Although facility and regional practices differed, positive test results were captured regardless of whether a patient was assessed in the dialysis clinic, or at a testing center, or at a hospital. In accordance with guidance from Centers for Disease Control and Prevention at the time,[79] prior to each treatment, patients were identified for testing by the dialysis staff through screening for recent exposure to a known COVID-19 patient, travel history to an endemic area, and/or symptoms of cough, dyspnea, fever, sore throat, and unexplained oxygen saturation <92%. Of note, only one DCI clinic performed routine RT-PCR screening of COVID-19 status in dialysis patients regardless of screening results. All patients with a positive SARS-CoV-2 test were defined as having COVID-19. Patients without a positive SARS-CoV-2 test were considered to be without COVID-19. Procedures regarding isolation varied by center and by whether COVID-19 was suspected or confirmed, reflecting local resources and availability of isolation rooms. Depending on availability, many clinics cohorted patients with COVID-19 together, often on a dedicated COVID-19 shift, either at that facility or at a nearby clinic, while others treated those with suspected or confirmed COVID-19 in isolation rooms with dedicated staff. Universal masking policies were adopted in all clinics by the end of March.

Demographic, comorbid, and clinical information including emergency department and/or hospitalization events and death reports (Centers for Medicare & Medicaid Services form 2746) were obtained from DCI’s proprietary outpatient electronic health record. Patient characteristics obtained from the electronic health record included age, sex, race, ethnicity, dialysis vintage, dialysis modality, treatment at an urban or rural clinic, use of a central venous catheter, living in a congregate setting at the time of diagnosis (e.g. nursing home, skilled nursing facility, or rehabilitation facility), body mass index, the number of comorbid conditions and specific comorbid conditions (e.g. diabetes mellitus, hypertension, congestive heart failure, atherosclerotic heart disease, cerebrovascular disorders, other cardiac diseases, chronic obstructive pulmonary disease, peripheral vascular disease, cancer), history of limb amputation, use of a wheelchair, need for assistance to perform activities of daily living, alcohol abuse, drug abuse, tobacco use, vaccination for influenza during the 2019-2020 flu season, documented pneumococcal vaccination, serum albumin most proximate to diagnosis, and use of selected medication groups (e.g. angiotensin converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs], inhaled respiratory agents [any anticholinergic, beta-agonist, and/or corticosteroid inhaler], or corticosteroids).

Primary outcomes of interest were diagnosis of COVID-19, and, among those with COVID-19, all-cause death within 90 days of COVID-19 diagnosis as compared to those without a diagnosis of COVID-19. Among those patients without COVID-19, all-cause death was defined by death within 90 days of the first COVID-19 diagnosis at the source clinic. All available electronic records delineating potential cause(s) of deaths were reviewed by two investigators (ECL and EL, Jr.) to determine primary events leading to death as well as any delineation of the potential role of COVID-19. Furthermore, although hospitalization records were not routinely available, the time course of illness and relevant time to events were tracked through documented dates of COVID-19 diagnosis, hospital admission, hospital discharge, and death. Patients were followed until death or 90 days, whichever came sooner, through September 1, 2020.

Two sets of analyses were conducted. The first analysis explored risk factors for acquiring COVID-19 among dialysis patients, whereas the second analysis explored risk factors for death among the subset of dialysis patients with COVID-19. Factors associated with a COVID-19 diagnosis were assessed by using univariate logistic regression analyses, using the list in the previous paragraph. The comparator group included all patients without COVID-19 diagnoses treated in the origin clinics of the COVID-19 cases; clinics with no COVID-19 cases through June 1, 2020 were excluded from the comparator group. This approach was chosen to minimize the influence of geographic factors in models because COVID-19 prevalence varied greatly across the country during the study period. Quantitative variables were presented as means ± SD and medians. For simplicity, age was represented as decades between 50 and 80 years old. For albumin, concentrations were categorized as severe hypoalbuminemia <3.5 g/dL, mild to moderate hypoalbuminemia (3.5 to 3.9 g/dL), and normal (≥4.0 g/dL). In addition to age, sex, and race, variables that were pre-specified *a priori*, only candidate variables significant at $p<0.1$ were included in multivariable analyses. Similarly, logistic regression models were constructed among patients with COVID-19 to assess patient characteristics related to mortality from COVID-19. Subgroup analyses were performed by stratifying on residence in a congregate setting. For consistency in comparisons, multivariable analysis of these subgroups incorporated the same variables used in the multivariable analysis of the aggregate. Statistical significance was defined as $p \leq 0.05$.

This retrospective de-identified evaluation was performed under exemption from informed consent through the DCI “Chronic Kidney Disease Quality Improvement and Clinical Outcomes” evaluation process, through the Western Institutional Review Board (WIRB, www.wirb.com). All statistical analyses were performed using SAS v.9.4 (www.sas.com). We used t-tests, analysis of variance (ANOVA) and chi square tests to compare data for most continuous, categorical and dichotomous variables, respectively, by COVID-19 status. Exceptions were use of the Kruskal-Wallis test for dialysis vintage and body mass index, and use of the Fisher’s exact test for assistance with ADLs.

3.3 Results

A total of 438 maintenance dialysis patients had diagnoses of COVID-19 during the 15-week study period, representing approximately 3% of 15,200 patients treated in 260 DCI clinics. Not all states and DCI clinics were exposed to COVID-19 during this early surge; the true denominator included patients from 96 clinics from 22 states with at least 1 affected patient, comprising 52% of all DCI patients (Figure S3.1). Therefore, these patients represented 438 of 7,948 (5.5%) of the dialysis population in impacted clinics. Comparing to patients without COVID-19 in these clinics, dialysis patients with COVID-19 were older, more likely to be of Black race, more likely to be treated with in-center hemodialysis, more likely to be treated at an urban clinic, more likely to use respiratory inhalers, and more likely to reside in a congregate setting (e.g. nursing home). Additionally, those with COVID-19 had a higher burden of comorbidity, with higher prevalence of cardiovascular diseases, diabetes, and requirement for assistance with ADLs and/or use of a wheelchair (Table 3.1).

Table 3.1. Characteristics and mortality of patients with and without diagnosed COVID-19 from DCI dialysis facilities with at least one affected patient from February – June 2020.

	COVID+	Non-COVID	p-value
	438 (5.5%)	7,510 (94.5%)	
Age	65.2 ± 13.2 (67.0)	62.0 ± 14.9 (63.4)	**<0.001**
<50	54 (12.3%)	1,527 (20.3%)	
51-59	91 (20.8%)	1,544 (20.6%)	
60-69	124 (28.3%)	2,023 (26.9%)	
70-79	114 (26.0%)	1,608 (21.4%)	
80+	55 (12.6%)	808 (10.8%)	
Male	264 (60.3%)	4,281 (57.0%)	0.2
Race			**<0.001**
White	115 (26.3%)	2,741 (36.5%)	
Black	253 (57.8%)	3,426 (45.6%)	
Other/Not Stated	70 (16.0%)	1,343 (17.9%)	
Ethnicity			0.6
Hispanic	37 (8.5%)	597 (8.0%)	
Non-Hispanic	335 (76.5%)	5,653 (75.3%)	
Not Stated	66 (15.1%)	1,260 (16.8%)	
Vintage	56.0 ± 55.4 (39.4)	54.9 ± 58.2 (36.9)	0.2
<3 months	29 (6.6%)	536 (7.1%)	
3-12 months	51 (11.6%)	1,028 (13.7%)	
12-36 months	120(27.4%)	2,137(28.5%)	
>36 months	238 (54.3%)	3,809 (50.7%)	
Home Dialysis Modality	18 (4.1%)	1,070 (14.3%)	**<0.001**
Urban Clinics	412 (94.1%)	6,613 (88.1%)	**<0.001**
Central Venous Catheter	104(23.7%)	1,621(21.6%)	0.3
Congregate Setting	239 (54.6%)	511 (6.8%)	**<0.001**
Albumin	3.8 ± 0.4 (3.8)	3.9 ± 0.4 (3.9)	**<0.001**
<3.5 g/dL	84 (19.2%)	1,037 (13.8%)	
3.5 to 3.9 g/dL	184 (42.0%)	2,853 (38.0%)	
4+ g/dL	147 (35.8%)	3,365 (44.8%)	
Body Mass Index	29.0 ± 7.5 (27.5)	28.5 ± 7.5 (27.2)	0.1
Tobacco Use	72 (16.4%)	1,230 (16.4%)	0.9
ACEi/ARB Use	141 (32.2%)	2,430 (32.4%)	0.9
Inhaled Respiratory Agents	109 (24.9%)	1,503 (20.0%)	**0.01**
Corticosteroids	27 (6.2%)	557 (7.4%)	0.3
Pneumonia Vaccine	385 (87.9%)	6,531 (87.0%)	0.6
2019 Influenza Vaccination	362 (82.7%)	6,072 (80.9%)	0.4
Comorbidity	3.3 ± 1.9 (3.0)	3.0 ± 1.8 (3.0)	**0.003**
Diabetes Mellitus	306 (69.9%)	4,367 (58.2%)	**<0.001**
Hypertension	346 (79.0%)	6,208 (82.7%)	**0.05**
CHF	104 (23.7 %)	1,580 (21.0%)	0.2
Atherosclerotic Heart Disease	118 (26.9%)	1,650 (22.0%)	**0.02**
Stroke	51 (11.6%)	665 (8.9%)	**0.05**
Other Cardiovascular	162 (37.0%)	2,550 (34.0%)	0.2
COPD	66 (15.1%)	1,053 (14.0%)	0.5
PVD	68 (15.5%)	1,115 (14.9%)	0.7
Amputation History	14 (3.2%)	182 (2.4%)	0.3
Assistance with ADL	4 (0.9%)	25 (0.3%)	0.07
Cancer History	36 (8.2%)	6161 (8.2%)	0.9
Alcohol Abuse History	56 (12.8%)	907 (12.1%)	0.7
Drug Abuse History	29 (6.6%)	427 (5.7%)	0.4
Wheelchair Use	15 (3.4%)	147 (2.0%)	**0.03**
Death	109 (24.9%)	275 (3.7%)	**<0.001**
Days to Death	16.7 ± 17.1 (11.0)	43.4 ± 26.7 (45.0)	**<0.001**

Note: Data are reported as mean ± standard deviation (median) or %. Age is reported in years and dialysis duration (vintage) in months. Race and ethnicity are independent of each other. We used T-test, ANOVA, and chi square tests to compare data for most continuous, categorical and dichotomous variables, respectively, by COVID-19 status; the exceptions are use of the Kruskal-Wallis test for vintage and body mass index, and use of the Fisher's exact test for assistance with ADL.

In multivariable models, risk factors associated with COVID-19 infection in maintenance dialysis included male sex, Black race, treatment at an urban clinic, residence in a congregate setting, comorbid conditions, and carrying a diagnosis of atherosclerotic heart disease and diabetes. By contrast, individuals treated with home dialysis were less likely to have COVID-19 infection (Table 3.2).

Table 3.2. Association between clinical characteristics and COVID-19 diagnoses among dialysis patients

	OR (95% CI)	**p-value**
Age		
60-69 y	1.14 (0.8-1.64)	0.5
70-79 y	1.14 (0.78-1.65)	0.5
≥80	1.16 (0.75-1.78)	0.5
Male Sex	1.35 (1.09-1.68)	0.01[a]
Black Race vs. White Race	1.95 (1.51-2.5)	<0.001[a]
Other Race vs. White Race	1.27 (0.91-1.77)	0.2
Home Dialysis	0.51 (0.31-0.82)	0.01[a]
Urban Clinics	2.3 (1.5-3.52)	0.001[a]
Congregate Setting	17.1 (13.51-21.54)	<0.001[a]
Albumin <3.5 g/dL	0.88 (0.66-1.17)	0.3
Inhaled Respiratory Agent	1.15 (0.89-1.49)	0.3
No. of Comorbidities[b]	0.89 (0.81-0.97)	0.01[a]
Diabetes Mellitus	1.36 (1.06-1.75)	0.02[a]
Hypertension	0.91 (0.67-1.22)	0.5
Atherosclerotic Heart Disease	1.42 (1.04-1.94)	0.03[a]
Stroke	1.03 (0.72-1.47)	0.9
Assistance with ADL	1.33 (0.39-4.48)	0.7
Wheelchair Use	0.89 (0.48-1.66)	0.7

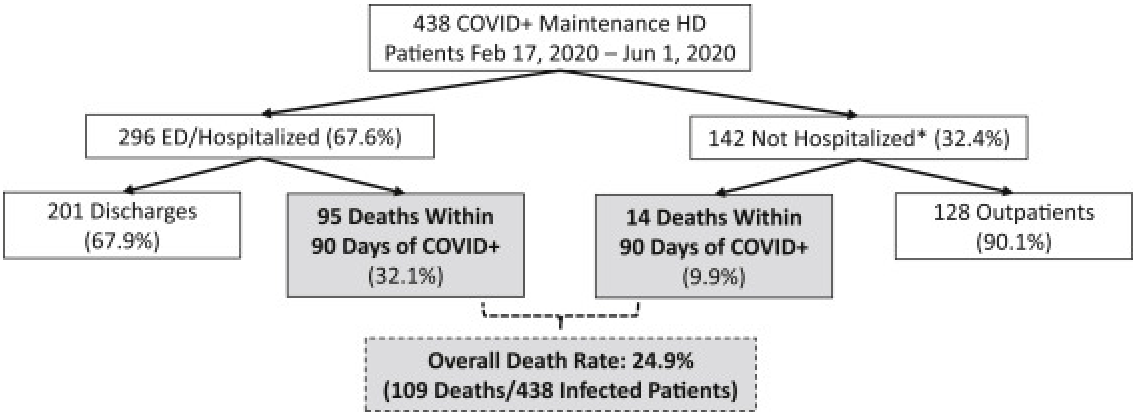
Entry in the logistic model requires $P < 0.1$ in univariate analysis, except for sex, which was forced in. N = 7,948.

[a] Statistically significant

[b] Relative risk per additional comorbid illness category among comorbidities listed in Table 3.1

All 438 dialysis patients with diagnoses of COVID-19 were either followed until death or censored at 90 days. Death occurred in 109 of 438 COVID-19 patients (24.9%), compared to 275 of 7510 (3.7%) of the non-COVID-19 cohort (Table 3.1, Figure 3.1). Among the 438 patients diagnosed with COVID-19, 296 patients (67.6%) received emergency department (ED) and/or inpatient hospital care either at the time of diagnosis or within 30 days following diagnosis (Figure 3.1). Of those 296 patients, 95 (32.1%)

Figure 3.1. The patient flowchart tracks the clinical course of maintenance dialysis patients with SARS-CoV-2 infection (diagnosed COVID-19) treated in DCI clinics.



*Hospitalization was defined as being in the ED or hospital on the date of COVID-19 diagnosis or within 30 days thereafter.

died. Of these 95 deaths, 86 deaths occurred during hospitalization, and 9 deaths occurred after initial hospital discharge. The remaining 201 (67.9%) patients with a hospital encounter were considered recovered by the end of follow-up. Among the 142 (32.4%) patients who were not initially hospitalized, 14 died within 30 days of diagnosis (8 in nursing homes, 2 in hospice, 2 with unknown site of death, and 2 at home), and another 9 patients were hospitalized 30 days or more after diagnosis. Three of these 9 patients were admitted due to COVID-19, while the other 6 received inpatient care for various medical conditions including vascular access issues. All 128 surviving outpatients were considered recovered from COVID-19 as of the end of follow-up.

Among the 296 patients who went to the ED or hospital, including 25 patients who received diagnoses while hospitalized, more than half the patients were tested upon arrival to the ED or on the day of inpatient admission, with diagnosis based on results of that test. Thus, although the average time from COVID-19 diagnosis to hospitalization was 2.8 ± 5.9 days (range 1-28 days), the median time corresponded to the first day. The overall length of stay after COVID-19 diagnosis for all hospitalized patients was 10.8 ± 10.7 days, with a median length of stay of 8 (IQR: 4, 14) days. Among patients who survived until discharge, length of stay was 11.1 ± 11.7 days, with a median length of stay of 8 (IQR: 4, 13) days.

Among the 109 patients who died, the mean time to death was 16.7 ± 17.1 days, with the median being 11 (IQR: 5.5, 22) days; one patient died in the ED. Approximately half the deaths had COVID-19 mentioned specifically as the primary or secondary cause of death, with additional notes in the electronic health records for all but six patients indicating that COVID-19 may have contributed to death. Of those 6 patients, one-half had a death date with no documented information surrounding the death. Immediate cause of death was most often attributed to pulmonary causes (51.9%), followed by cardiac (9.3%), and a combination of cardiac and pulmonary causes (7.4%). There were 8.3% of cases that specifically mentioned infection/sepsis and 2.8% due to hemorrhage. There were 20 deaths (18.5%) with the primary cause described only as cardiopulmonary arrest without further information or no information surrounding death circumstances recorded at all. Overall, 10 patients withdrew from dialysis (6 residing in a nursing home, 3 while in the hospital, and 1 at home), 9 of whom received hospice care prior to death.

Characteristics of patients who died compared to those who survived are shown in Table 3.3. Older patients had higher mortality, particularly those over 80 years old. Comorbidity related to chronic heart failure, hypertension, and other cardiovascular diseases as well as peripheral vascular disease, low albumin level, and use of a

Table 3.3. Characteristics of patients with documented COVID-19 by vital status.

	Died	**Survived**
	109 (24.9%)	329 (75.1%)
Age	70.8 ± 10.3 (70.5)	63.3 ± 13.6 (64.2)
<50	2 (1.8%)	52 (15.8%)
51-59	17 (15.6%)	74 (22.5%)
60-69	34 (31.2%)	90 (27.4%)
70-79	33 (30.3%)	81 (24.6%)
80+	23 (21.1%)	32 (9.7%)
Male	70 (64.2%)	194 (59.0%)
Race		
White	36 (33.0%)	79 (24.0%)
Black	56 (51.4%)	197 (60.0%)
Other/Not Stated	17(15.6%)	53(16.1%)
Ethnicity		
Hispanic	10 (9.2%)	27 (8.2%)
Non-Hispanic	87 (79.8%)	248 (75.4%)
Not Stated	12 (11.0%)	54 (16.4%)
Vintage	63.4 ± 61.6 (43.6)	53.6 ± 53.0 (39.3)
<3 months	5 (4.6%)	24 (7.3%)
3-12 months	10 (9.2%)	41 (12.5%)
12-36 months	28(25.7%)	92(28.0%)
>36 months	66(60.6%)	172(52.3%)
Home Dialysis Modality	3(2.8%)	15(4.6%)
Central Venous Catheter	30(27.5%)	74(22.5%)
Congregate Setting	65(59.6%)	174(52.9%)
Urban Clinics	103(94.5%)	309(93.9%)
Albumin	3.7 ± 0.5 (3.7)	3.8 ± 0.4 (3.9)
<3.5 g/dL	28 (25.7%)	56 (17.0%)
3.5 to 3.9 g/dL	45 (41.3%)	139 (42.3%)
4+ g/dL	36 (33.0%)	121 (36.8%)
Body Mass Index	28.9 ± 6.9 (26.9)	29.1 ± 7.7 (27.5)
Tobacco Use	19 (17.4%)	53 (16.1%)
ACEi/ARBs	28 (25.7%)	113 (34.4%)
Inhaled Respiratory Agents	35 (32.4%)	74 (22.5%)
Corticosteroids	12 (11.0%)	15 (4.6%)
Pneumonia Vaccine	94 (86.2%)	291 (88.5%)
2019 Influenza Vaccination	88 (80.7%)	274 (83.3%)
Comorbidity	3.7 ± 2.2 (3.0)	3.2 ± 1.8 (3.0)
Diabetes Mellitus	75 (68.8%)	231 (70.2%)
Hypertension	79 (72.5%)	267 (81.2%)
CHF	37 (33.9%)	67 (20.4%)
Atherosclerotic Heart Disease	33 (30.3%)	84 (25.8%)
Stroke	13 (11.9%)	38 (11.6%)
Other Cardiovascular	53 (48.6%)	109 (33.1)
COPD	19 (17.4%)	47 (14.3%)
PVD	29 (26.6%)	39 (11.9%)
Amputation History	5 (4.6%)	9 (2.7%)
Assistance with ADL	2 (1.8%)	2 (0.6%)
Cancer History	11 (10.1%)	25 (7.6%)
Alcohol Abuse History	13 (11.9%)	43 (13.1%)
Drug Abuse History	5 (4.6%)	24 (7.3%)
Wheelchair Use	8 (7.3%)	7 (2.1%)

Note: Data are reported as mean ± standard deviation (median) or %. Age is reported in years and dialysis duration (vintage) in months. Race and ethnicity are independent of each other.

wheelchair were more prevalent in patients who died. In multivariable models, older age became strongly associated with death, with increased risk in each decade after age 50, along with peripheral vascular disease, congestive heart failure, hypertension, and wheelchair use remaining significantly associated with mortality risk (Table 3.4).

Table 3.4. Association between clinical characteristics and all-cause death among dialysis patients with COVID-19

	OR (95% CI)	P
Age category		
<50 y	1.00 (reference)	
50-59 y	5.57 (1.18-26.39)	0.03[a]
60-69 y	8.52 (1.87-38.8)	0.01[a]
70-79 y	9.48 (2.07-43.37)	0.004[a]
80+ y	15.55 (3.25-74.34)	0.001[a]
Male Sex	1.25 (0.75-2.08)	0.4
Black Race vs. White Race	0.69 (0.4-1.2)	0.2
Other Race vs. White Race	0.68 (0.32-1.43)	0.3
Congregate Setting	0.91 (0.55-1.52)	0.7
Albumin <3.5 g/dL	1.37 (0.77-2.46)	0.3
ACEi/ARBs	0.78 (0.45-1.33)	0.4
Inhaled Respiratory Agent	1.33 (0.75-2.36)	0.3
Corticosteroid	2.19 (0.89-5.37)	0.09
Number of Comorbidity	0.86 (0.68-1.09)	0.2
Hypertension	0.5 (0.26-0.96)	0.04[a]
Congestive Heart Failure	1.95 (1.04-3.65)	0.04[a]
Other Cardiovascular	1.74 (0.88-3.43)	0.1
Peripheral Vascular Disease	3.12 (1.59-6.14)	0.001[a]
Wheelchair Use	3.36 (1.05-10.78)	0.04[a]

Entry in the logistic model requires P < 0.1 in univariate analysis, except for sex, which was forced in. N = 438.

[a]Statistically significant

In subgroup analysis with stratification by residence in a congregate setting, 199 of 7198 (2.8%) of patients in noncongregate settings had COVID-19, compared to 239 of 750 (31.9%) among residents of congregate settings. Of those with COVID-19, noncongregate mortality was 22.1% and congregate mortality was 27.2% (Tables S3.1-S3.2). Multivariable analysis of the subgroups showed risk factors for COVID-19 to be similar to risk factors identified in aggregate analysis (Tables S3.3-S3.4).

3.4 Discussion

Maintenance dialysis patients were found to be at high risk of developing COVID-19, and among those with COVID-19, 90-day mortality approached 25%. Of note, the current study extended outcome follow-up to 90 days, compared to most initial reports that covered only early and short-term outcomes. Among dialysis patients, key risk factors for COVID-19 included residence in a long-term care facility, Black race, male sex, diabetes, receipt of in-center compared to home dialysis, and treatment at an urban dialysis center. In dialysis patients who develop COVID-19, older age, hypertension, congestive heart failure, peripheral vascular disease, and wheelchair use were associated with higher risk of death.

Studies have shown a close interrelationship between socioeconomic status and health outcomes, further exacerbated by systemic racial biases.[80] The ability to maintain physical distancing through low household density, working from home, or accepting a loss of income, is a matter of privilege and more often the territory of more affluent communities. In contrast, urban areas of high density, which tend to have a greater non-White population, reflect communities in which a pandemic is more likely to take hold,[67] highlighted by a higher prevalence of medical comorbid conditions. That our study shows worse outcomes with non-White race, more comorbid conditions, and treatment at urban dialysis centers reflects this tangle of many factors. Of note, unlike in the general population, Hispanic ethnicity was not associated with either risk of acquiring COVID-19 or risk of mortality in patients with COVID-19. It is possible that the locations of DCI clinics with COVID-19 patients generally had a lower proportion of people who identify as Hispanic or that missing ethnicity data impacted results.

Among dialysis patients, those also residing in a congregate setting had more than 17-fold higher rate of COVID-19 compared to those residing independently, a pattern that, although commented on, has not been well quantified in national studies.[23,81] In congregate residences such as group homes and nursing facilities, the capacity to isolate COVID-positive patients is often limited, staffing may be stretched as employees fall ill, and staff members carry infectious risk to the community when they leave the facility. There may be a role for universal screening in such congregate settings, particularly when at least one case is identified.[22] Moreover, patients living in congregate settings are often older and more likely to be frail; the association between mortality and markers of frailty such as age, peripheral vascular disease, and decreased mobility shows that COVID-19 in the congregate setting is all the more damaging.

Reflecting these factors, communities with dense urban populations, Black and Hispanic neighborhoods, and high numbers of nursing home residents have the greatest need for support during this pandemic. Measures such as expanded testing, community education, promoting capacity for telemedicine and financial support to facilitate physical distancing would reduce transmission. Because a large proportion of dialysis patients derive from these communities, nephrologists have a responsibility to advocate better disease containment and greater relief for these communities. Furthermore, compared to other disadvantaged groups, dialysis patients almost constantly interface with the health care system; accordingly, public health departments can and should coordinate with dialysis providers to provide interventions such as expanded testing and possibly vaccination prioritization.

The mandatory congregate settings and the associated commutes can create additional exposure risk for the majority of dialysis patients, as demonstrated by the increased risk associated with in-center dialysis relative to home dialysis. Patients performing home dialysis tend to be younger and healthier than patients treated by in-center hemodialysis.[69] For in-center hemodialysis patients, enhanced and universal sanitation protocols are a necessity, including for the transportation services involved, and dialysis facilities have taken steps to protect patients, including emptying waiting rooms, screening patients for symptoms and isolating those who screen positive, increasing spacing within dialysis facilities and implementing universal masking for patients and staff.[16,82] Indeed, while transmission of COVID-19 has been demonstrated to occur in congregate settings such as in nursing homes, it has seldom been reported to occur within the outpatient dialysis clinic, where infection control precautions are closer to those in the hospital setting than those of nursing homes. Our experience underscores the very high risk of infection in dialysis patients residing in congregate facilities, emphasizing the need to view these patients as high risk and potential candidates for enhanced screening, including asymptomatic testing, and highlighting the critical need for improved communication between long-term care facilities and dialysis facilities. Critically, the COVID-19 pandemic has emphasized the need to increase the use of home dialysis and kidney transplantation for treatment of kidney failure.

Improving outcomes in patients with COVID-19 requires particular attention in the dialysis population, focusing on prevention of SARS-CoV-2 infection as well as evaluation of vaccines and novel treatments in the vulnerable dialysis population. Although COVID-19 care in dialysis patients remains largely supportive, practices implemented at the systems level can be impactful. Similar to other studies,[75,77] we observed that approximately 60% of COVID-positive dialysis patients were hospitalized, translating to a need for adequate resource planning for in-hospital dialysis equipment, consumables, and staffing to minimize strain, particularly given the associated system strain with the high incidence of acute kidney injury requiring dialysis among critically ill COVID-19 patients. With admissions averaging eleven days' duration in an already-frail population, a number of patients may be expected to need rehabilitation; therefore coordination among hospitals, dialysis centers, rehabilitation facilities and long-term care facilities is critical to avoid medical errors and readmissions. In early studies, COVID-19 survivors presented a spectrum of persistent pulmonary dysfunction, and they are expected to have a high prevalence of post-intensive care syndrome, which encompasses reduced physical, cognitive, and mental health after critical illness.[83] Therefore maintenance dialysis patients who survive COVID-19 may benefit from interdisciplinary post-hospitalization care. Also, this study and others demonstrate that mortality exceeds 20% among maintenance dialysis patients.[75–77,84,85] Therefore discussions around advance care planning should be considered to avoid aggressive medical therapy when it is incongruent with the patient's life goals and values; this is particularly true of those with advanced age and with other indicators of frailty, which were associated with mortality in our study. The appropriate planning for and implementation of palliative care and hospice is critical in this population, particularly with the devastating impact of acute illnesses like COVID-19.

Our study of the COVID-19 pandemic in the outpatient dialysis setting uses a large population derived from a national dialysis provider with longitudinal patient follow-up for outcomes. We nevertheless acknowledge the study's limitations. It focuses on observational data acquired from the dialysis provider, rendering specific details surrounding in-hospital events less available. Second, very limited testing availability, particularly in March through June 2020, may have resulted in underestimation of COVID-19 cases and misclassification of deaths. Third, given the extensive comorbid condition burden in dialysis patients with COVID-19, determining the cause of death in this population remains somewhat subjective, and we have restricted analyses to all-cause death. Fourth, we excluded dialysis clinics with no COVID-19 cases to facilitate comparison between COVID and non-COVID patients. This may result in other biases being introduced into models, and this restriction prevents comparisons with geographic regions where COVID-19 incidence was very low during this early pandemic surge, (i.e., where COVID-19 cases were unlikely in the dialysis clinic). Fifth, because our study defined all patients with a positive SARS-CoV-2 test as having COVID-19, we did not distinguish asymptomatic carriers from those with symptomatic disease; currently, the impact of SARS-CoV-2 vaccines on asymptomatic carriage and transmission is unknown, so this distinction will need greater investigation and scrutiny as vaccinations occur. Sixth, we found very few home dialysis patients diagnosed during this period, which may be due in part to more frequent opportunities for screening and testing for the in-center hemodialysis population. However, we note that there are far fewer home dialysis patients living in congregate settings and overall testing capacity was very limited during this time frame, so symptomatic patients were likely to be brought to the ED and/or be hospitalized, potentially mitigating this issue.

In conclusion, dialysis patients are at high risk of COVID-19, with 5.5% of patients with a diagnosis of COVID-19 in facilities with at least one COVID-19 case during the first 3 months of the pandemic in the United States. In-center dialysis, residence in a long-term care facility and Black race are all major risk factors associated with COVID-19, suggesting that the ability to maintain physical distance is critical to controlling COVID-19. Mortality among dialysis patients with COVID-19 exceeds 20%. To address COVID-19 while awaiting availability of safe and effective vaccines and therapeutics, dialysis facilities should recognize risk factors, maximize utility of telemedicine, promote home dialysis, encourage transplantation where appropriate, and optimize socioculturally adapted education regarding physical distancing and universal precautions including masking, not limited to the dialysis clinic but relevant to all other at-risk settings.

Chapter 4: Epidemiology and Outcomes of COVID-19 in Home Dialysis Patients Compared with In-Center Dialysis Patients[86]

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[86] Hsu CM, Weiner DE, Aweh G, Salenger P, Johnson DS, Lacson E. Epidemiology and Outcomes of COVID-19 in Home Dialysis Patients Compared with In-Center Dialysis Patients. *J Am Soc Nephrol*. 2021;32(7):1569-1573. doi:10.1681/ASN.2020111653

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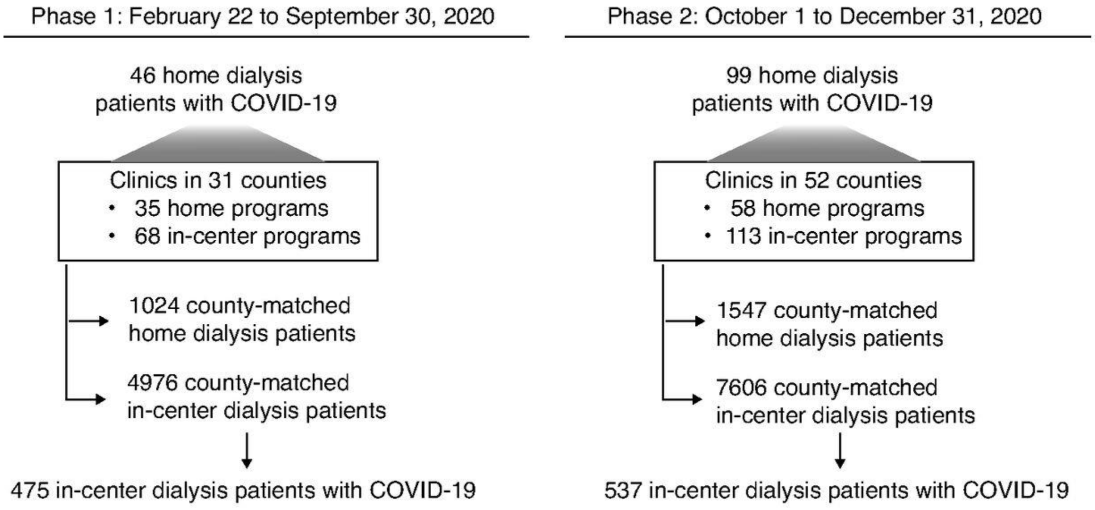
4.1 Introduction

Patients on dialysis are particularly vulnerable to coronavirus disease 2019 (COVID-19), with multiple studies describing mortality >20%.[64,87,88] Although infection rates among patients on dialysis tend to parallel local patterns, this population has a higher rate of COVID-19 compared with the general population; this may be a reflection of increased symptom screening and testing, and a limited ability to achieve physically distancing, particularly given dependence of most patients on maintenance dialysis in the United States on in-center hemodialysis.[69] Studies describing COVID-19 in patients receiving home dialysis are lacking but needed, given they share with patients on in-center dialysis similar risk factors for poor outcomes, including possible impaired immunity and high prevalence of comorbid conditions.

4.2 Methods

Dialysis Clinic, Inc. (DCI) is a national not-for-profit dialysis provider serving approximately 2,000 patients on home dialysis (90% receiving peritoneal dialysis, 10% hemodialysis). The company has 116 clinics in 27 states with active home dialysis programs, although some of these clinics have only one or two patients on home dialysis. This retrospective cohort study included all DCI patients on home dialysis with positive testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from February 22, 2020 to December 31, 2020, with outcomes ascertained through February 1, 2021. Patients were diagnosed with COVID-19 via nasopharyngeal or oropharyngeal swab sent for reverse transcriptase polymerase chain reaction (RT-PCR) testing. All positive COVID-19 tests were captured, regardless of whether the patient was assessed in the dialysis clinic, at a testing center, or at a hospital, and all patients with a positive SARS-CoV-2 test were considered to have COVID-19. Demographic, comorbidity, and clinical data were collected from DCI's electronic health records. To reflect the evolving epidemiology of the COVID-19 pandemic, analyses were conducted for two time periods: February 22 to September 30, 2020 (termed "Phase 1") and October 1 to December 31, 2020 (termed "Phase 2"). For each phase, patients on home dialysis with COVID-19 were mapped to their clinics' counties, which were then used to identify and compare dialysis patients in both home and in-center programs located within the same counties (Figure 4.1). We conducted multivariable logistic regression analysis to assess risk factors for COVID-19 among patients on home dialysis using *a priori* identified covariates. To compare COVID-19 risk by modality, we calculated COVID-19 incidence rate was calculated for each modality, indexed to the date of the first COVID-19 case in a clinic's county, whether home or in-center. We also collected 30-day mortality rates,

Figure 4.1. Derivation of the study population in each phase of the study.



Home dialysis patients with COVID-19 were mapped to their clinics' counties, which were then used to identify dialysis patients in both home and in-center programs in the same counties. COVID-19 cases were additionally identified from this in-center dialysis population.

indexed to the date of COVID-19 diagnosis for patients with COVID-19 and indexed to first COVID-19 case in the clinic's county for patients without COVID-19. We conducted multivariable analysis with *a priori* identified covariates to assess risk factors for mortality among patients on home dialysis with COVID-19.

4.3 Results

In Phase 1, 46 of 1024 (4.5%) home dialysis patients were diagnosed with COVID-19, deriving from clinics in 31 counties (Figure 4.1; see map Figure S4.1). Among patients on home dialysis, Black race, Hispanic ethnicity, and long-term care facility (LTCF) residence were associated with COVID-19 (Table 4.1). Patients on in-center dialysis had

Table 4.1. Association between clinical characteristics and COVID-19 diagnosis among home dialysis patients

	Phase 1: Feb 22 – Sep 30, 2020			Phase 2: Oct 1 – Dec 31, 2020		
	Odds Ratio	95% Confidence Limits		Odds Ratio	95% Confidence Limits	
Age						
<50	Ref	---	---	Ref	---	---
50-59	0.79	0.32	1.93	0.87	0.47	1.61
60-69	0.82	0.36	1.88	0.88	0.50	1.55
70-79	1.03	0.42	2.50	0.94	0.51	1.74
80+	0.64	0.13	3.18	0.75	0.29	1.91
Male sex	0.95	0.51	1.75	0.76	0.50	1.15
Race						
White	Ref	---	---	Ref	---	---
Black	**3.23**	**1.55**	**6.74**	0.64	0.35	1.16
Other	1.40	0.57	3.43	1.27	0.78	2.09
Hispanic ethnicity	**5.08**	**1.93**	**13.38**	1.17	0.48	2.82
Number of comorbidities	0.90	0.49	1.66	1.01	0.66	1.53
Vintage						
≤ 1 year	Ref	---	---	Ref	---	---
1-3 years	0.61	0.29	1.26	0.81	0.50	1.31
>3 years	0.50	0.23	1.08	0.62	0.36	1.06
LTCF residence	**8.54**	**3.15**	**23.11**	2.19	0.81	5.95
Urban setting	0.41	0.13	1.29	**0.41**	**0.24**	**0.69**

Results of multivariable logistic regression models using *a priori* identified covariates a significantly higher incidence of COVID-19 that was attenuated after excluding LTCF residents (Table 4.2). In Phase 2, 99 of 1547 (6.4%) patients on home dialysis were diagnosed with COVID-19, deriving from clinics in 52 counties (Figure S4.1). The incidence of COVID-19 no longer differed significantly by modality. COVID-19 prevalence among patients in an LTCF declined from Phase 1 to Phase 2. Among patients not in an LTCF, COVID-19 prevalence rose among those receiving home dialysis but remained stable among those receiving in-center dialysis (Table 4.2).

Table 4.2. COVID-19 period prevalence and incidence rates of dialysis patients, matched to home dialysis patients with COVID-19 by county

	Phase 1: Feb 22 – Sep 30, 2020			Phase 2: Oct 1 – Dec 31, 2020		
	Home	In-center	p-value	Home	In-center	p-value
Prevalence, total	46 / 1024 (4.5%)	475 / 4976 (9.6%)	<0.001	99 / 1547 (6.4%)	537 / 7606 (7.1%)	0.34
Prevalence, LTCF only	7 / 34 (20.6%)	227 / 639 (35.5%)	0.10	5 / 44 (11.4%)	198 / 921 (21.5%)	0.13
Prevalence, non-LTCF only	39 / 990 (3.9%)	248 / 4337 (5.7%)	0.03	94 / 1503 (6.3%)	339 / 6685 (5.1%)	0.06
Incidence rate (cases per 1000 patient-months)	6.5	14.0		9.9	11.0	
Morbidity and Mortality of patients with COVID-19						
ED visit or Hospitalization	31 / 46 (67.4%)	326 / 475 (68.6%)	0.86	57 / 99 (57.6%)	340 / 537 (63.3%)	0.28
Mortality	6 / 46 (13.0%)	124 / 475 (26.1%)	0.06	12 / 99 (12.1%)	74 / 537 (13.8%)	0.78

Prevalence is reported as cases of COVID-19 / county-matched population (%).
Hospital utilization and mortality are within 30 days of COVID-19 diagnosis.

Among patients on home dialysis, 6 of 46 (13.0%) with COVID-19 died in Phase 1, and, 12 of 99 (12.1%) with COVID-19 died in Phase 2 (Table 4.2). This compares with 74 of 978 (7.6%) and 127 of 1448 (8.8%) of patients on home dialysis without COVID-19 in Phases 1 and 2, respectively (data not shown). Multivariable analysis conducted on the entire cohort (from February 22 through December 31) of patients on home dialysis with COVID-19 found that older age, longer vintage (dialysis duration), and cardiovascular disease were associated with mortality (Table 4.3).

Table 4.3. Risk factors for death among home dialysis patients with COVID-19 from February to December 2020

	Odds Ratio	95% Confidence Limits	
Age			
<50	Ref	---	---
50-59	1.63	0.10	27.50
60-69	7.85	0.92	67.10
70-79	**10.88**	**1.22**	**97.20**
80+	**48.58**	**3.17**	**744.60**
Male sex	0.51	0.15	1.73
Race			
White	Ref	---	---
Black	0.15	0.02	1.17
Other	1.47	0.37	5.95
Hispanic ethnicity	3.11	0.44	22.17
Number of comorbidities	0.49	0.12	2.02
Vintage			
≤ 1 year	Ref	---	---
1-3 years	3.89	0.85	17.75
>3 years	**9.79**	**1.73**	**55.44**
LTCF residence	5.43	0.95	31.10
Cardiovascular disease	**8.47**	**1.98**	**36.17**
Albumin <3.5 mg/dL	0.83	0.24	2.86

Results of a multivariable logistic regression model using *a priori* identified covariates

4.4 Discussion

Among patients on home dialysis, 4.5% had COVID-19 from February 22 through September 2020 with Black race, Hispanic ethnicity, and LTCF residence identified as significant risk factors, whereas from October through December 2020, 6.4% of patients on home dialysis had COVID-19. These analyses reflect the epidemiology of the COVID-19 pandemic in the United States over the past year. Early in the pandemic, testing constraints limited diagnoses to the symptomatic and those with easier access to health care, and COVID-19 was concentrated in LTCFs as well as urban communities, affecting a greater proportion of Black and Hispanic patients (Table S4.1).[67]

Over time, LTCFs and dialysis facilities implemented and improved infection control practices targeting SARS-CoV-2 transmission, and the pandemic broadened to also impact more rural areas of the country. Thus, the epidemiology of COVID-19 in patients on home dialysis reflects its evolution in the general community, paralleling COVID-19 in the general dialysis population.[87,89] Critically, the COVID-19 prevalence reported here may differ from prior reports due to both duration of the study period and inclusion of rural areas.[72,74,87,88] Moreover, COVID-19 prevalence in patients on home dialysis still exceeded that of the general population, which may be for multiple reasons. This population has greater-than-average healthcare utilization resulting from both ESKD and other medical comorbid conditions, a need for in-person medical care and, in some cases, the associated need for shared transportation that limits physical distancing ability. Because this patient population has more comorbid conditions, it may also have a lower threshold to seek testing. Of note, epidemiologic patterns influenced by community COVID-19 prevalence, described in the October through December phase, are likely to persist in the coming months.

The early difference in COVID-19 prevalence by modality may be attributable to multiple factors, including limited ability to effectively practice physical distancing and higher numbers and a higher proportion of LTCF residents with COVID-19 among patients on in-center dialysis. Additionally, particularly in Phase 1, when diagnostic testing resources were less available, patients receiving in-center dialysis likely encountered more opportunities for screening and testing. In phase 2, more widespread testing in the community provided an opportunity for greater diagnostic parity, although residual disparity may have persisted. In addition, LTCF residence was a significant contributor to in-center COVID-19 prevalence in Phase 1; lower COVID-19 rates among LTCF residents in Phase 2 appear associated with lower rates of COVID-19 among patients on in-center dialysis. These findings reinforce the importance of infection control practices and frequent testing, especially in high-risk congregate settings.

Patients on home dialysis likely have greater mortality risk from COVID-19, compared with the 2.2% mortality rate recently estimated among the general population.[90] Of note, the mortality rate in patients on home dialysis here was less than that reported by other studies of COVID-19 in the general dialysis population,[72,74,87,88] including an earlier study by this group;[64] this likely reflects the generally better health of patients on home dialysis compared to the overall dialysis population. Mortality decreased from Phase 1 to Phase 2, falling by half among the in-center population, which likely reflects expanded testing availability enabling diagnosis of milder cases, improvement in COVID-19 management over time, fewer infections in LTCF residents, and possibly a reduced inoculum burden with widespread masking.[91] Nevertheless, this high rate of poor outcomes in this vulnerable population reinforces the need for vaccine prioritization and continued vigilance in treating these patients. Older age and cardiovascular disease are known predictors of poor outcomes from COVID-19,[92] reflected in this study as well.

We acknowledge this study's limitations. Matching by county may have introduced certain biases, but this restriction critically mitigates the bias of COVID-19's geographic variation during the study period. Due to the study's observational design, we cannot exclude confounders when comparing outcomes by modality. It is also possible that the reduced differences in Phase 2 compared to Phase 1 were, at least in part, due to a larger study population, demonstrating a regression to the mean.

In conclusion, COVID-19 epidemiology among patients on home dialysis over time reflects community trends and is similar to the epidemiology among patients on in-center dialysis. This study reinforces previous findings that residence in an LTCF is a significant risk factor for infection. Although the COVID-19 case fatality rate among patients on home dialysis trends lower than that for in-center hemodialysis, it is still high, underscoring that preventing COVID-19 in the dialysis population remains critical.

Chapter 5: Seroresponse to SARS-CoV-2 vaccines among maintenance dialysis patients over six months[93]

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[93] Hsu CM, Weiner DE, Manley HJ, et al. Seroresponse to SARS-CoV-2 Vaccines among Maintenance Dialysis Patients over 6 Months. *Clin J Am Soc Nephrol*. Published online February 10, 2022:CJN.12250921. doi:10.2215/CJN.12250921
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5.1 Introduction

As of November 2021, the coronavirus disease 2019 (COVID-19) pandemic has claimed >5 million lives worldwide, with >750,000 deaths in the United States.[90] The three vaccines currently authorized for use by the Food and Drug Administration, either with approval or emergency use authorization, are all highly effective at preventing death and serious illness in the general population.[28–30]

Concerns about the robustness of the vaccine-induced immune response in vulnerable populations (Chemaitelly *et al*., unpublished data) [94,95] have prompted the Centers for Disease Control and Prevention (CDC) to recommend an additional dose for patients who are immunocompromised,[96] and concerns about the durability of response have prompted guidance on booster doses of vaccine.[97] Early studies suggest that the majority of patients receiving maintenance dialysis generate an appropriate initial seroresponse to mRNA vaccines, although at a lower rate than the general population.[98–105] Given that patients on maintenance dialysis have an attenuated response to other vaccines, with extensive data on additional or booster doses for hepatitis B vaccination,[31] similar concerns exist that potential uremia-associated immunocompromise may affect the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. A small study in 76 patients on dialysis demonstrated anti-spike IgG antibody decline in 75% of patients, with almost 20% becoming seronegative by 4 months (Dulovic *et al*., unpublished data). In the general population, waning immunity has been linked to increased breakthrough cases.[106,107] Given the very high risk for poor outcomes associated with COVID-19 in patients on maintenance dialysis, and their limited ability to physically distance, obtaining and maintaining immunity is of critical importance.[64,108] Therefore, we conducted a retrospective, multicenter study to assess the intermediate duration of vaccine-induced seroresponse among patients receiving maintenance dialysis. Expanding on an earlier publication,[99] we report here the seroresponse trends over time.

5.2 Methods

Dialysis Clinic, Inc. (DCI) is a national not-for-profit provider that cares for >15,000 patients at 260 outpatient dialysis clinics across 29 states. Since January 2021, physicians at DCI facilities have had available an antibody-monitoring protocol for patients, activated by physician order upon documentation of receipt of a SARS-CoV-2 vaccine, regardless of the vaccine type or place of administration. Like the existing hepatitis B vaccine protocol, the SARS-CoV-2 vaccine protocol documents seroresponse to vaccination by measuring antibody titers as part of the monthly blood draws. IgG spike antibodies (anti-spike IgG) against the receptor-binding domain of the S1 subunit of SARS-CoV-2 spike antigen were measured using the chemiluminescent assay ADVIA Centaur® XP/XPT COV2G, which received emergency use authorization in July 2020.[109] This semi-quantitative assay reports an Index Value between 0 and ≥20 established with calibrators; per manufacturer specifications, anti-spike IgG titer ≥1 Index represents detectable antibodies, likely signifying seroresponse.[109]

Demographic and clinical data, vaccination dates, and anti-spike IgG titer results were obtained from the DCI electronic health record. Patients were included if they had received a complete vaccine series of one vaccine type without additional doses. Patients were excluded from analysis if they were <18 years of age or did not have at least one antibody titer assessment ≥14 days after completion of a vaccine series (hereafter termed "fully vaccinated" in accordance with current CDC guidelines[110]). Baseline characteristics were assessed at the time of full vaccination. Prior COVID-19 was defined by a positive SARS-CoV-2 PCR test at any time before the date of full vaccination or anti-spike IgG titer ≥1 Index before or within 10 days after the first vaccine dose (representing likely prior undiagnosed COVID-19, as suggested by prior studies[28,111]). Through a DCI protocol which has been active since March 2020, positive SARS-CoV-2 tests were captured regardless of whether the patient was assessed in the dialysis clinic, at a testing center, or at a hospital. Antibody test results were captured from only the DCI dialysis clinics. Analyses were stratified by prior COVID-19 status.

In analyses, anti-spike IgG titers were grouped by the month of assessment relative to the date of full vaccination (month 1, 2, etc). Primary descriptive analyses compared titers by vaccine type over time. To assess whether initial vaccine response was associated with sustained response, secondary descriptive analyses compared trends over time, stratifying by the maximum titer attained during the first two months following full vaccination ("maximum initial titer"). Handling of missing and duplicate values is described in the Supplemental Item S5.1.

To better characterize antibody levels over time, time-to-event analysis was used to assess for the outcome of antibody titer <1 Index or development of COVID-19, defined as having a positive SARS-CoV-2 test. Two sets of sensitivity analyses were conducted.

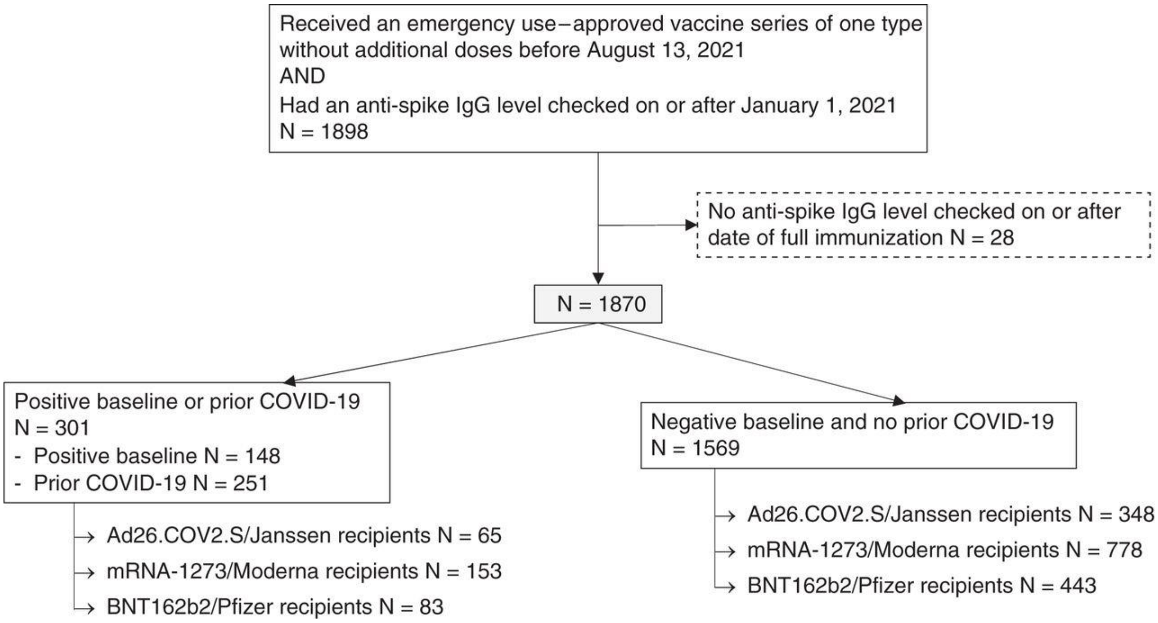
The first used the outcome of antibody titer <2 Index or development of COVID-19, using a threshold suggested by DCI Lab's internal validation methods.[99] The second used the outcome of antibody titer <1 Index alone. Of note, all patients dialyzing in DCI facilities are screened for COVID-19 symptoms and recent exposure upon arrival to the dialysis facility for each treatment, followed by SARS-CoV-2 testing if they screen positive. Patients were censored at death, transplantation, administration of an additional vaccine dose (third dose or booster dose), or last available titer assessment. Results were compared by vaccine type and by maximum initial titer in descriptive analyses. The association of patients' clinical characteristics with time to the outcome was assessed using multivariable Cox proportional hazards regression; covariates were selected *a priori* on the basis of on clinical relevance and availability in the dataset.

This study was reviewed and approved by the WCG Institutional Review Board Work Order 1-1456342-1. Statistical analyses were performed using R version 4.0.2.

5.3 Results

Among patients receiving maintenance dialysis at a DCI facility, 1898 adults across 142 clinics received a full SARS-CoV-2 vaccine series and had at least one anti-spike IgG titer assessment after January 1, 2021, with 1870 patients having anti-spike IgG assessment after full vaccination (Figure 5.1). Of these, 1087 (58%) were men, 438 (23%) were Black, 301 (16%) were Hispanic, and the average±SD age was 64±14 years; 301 (16%) patients had a history of COVID-19 on the basis of either early positive anti-spike IgG levels or prior clinical diagnosis. Antibody assessment tended to be clustered by clinic, with 80% of patients being treated in 30 DCI clinics. Recipients of

Figure 5.1. Flow diagram of 1870 patients included in the study.



Baseline defined as anti-spike IgG titer >1 Index before or within 10 days after first dose of vaccine; prior coronavirus disease 2019 (COVID-19) defined as positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test before full immunity (at 14 days after completion of a vaccine series).

BNT162b2/Pfizer tended to be older and have longer follow-up, whereas recipients of Ad26.COV2.S/Janssen were more often of Black race. Among the 1569 patients without a history of COVID-19, a higher proportion of mRNA-1273/Moderna recipients were receiving peritoneal dialysis compared with recipients of BNT162b2/Pfizer and Ad26.COV2.S/Janssen (Table 5.1).

Patients without a history of COVID-19 who received an mRNA vaccine had declining anti-spike IgG titers over time (Figure 5.2A). Among BNT162b2/Pfizer recipients, median [IQR; N number of data values] antibody titer was ≥20 [5.89, ≥20; N of 340] Index in month 1 following full vaccination, with a reduction to 3.16 [0.82, 10.59; N of 379] by month 4 and 1.96 [0.60, 5.88; N of 244] Index by month 6. Among recipients of

Table 5.1. Baseline patient characteristics by history of COVID-19 and type of vaccine received.

	All vaccinated DCI patients [a]	Study patients						
			No history of COVID-19 (N=1569)			History of COVID-19 (N=301)		
		Overall	Ad26.COV2.S/ Janssen	mRNA-1273/ Moderna	BNT162b2/ Pfizer	Ad26.COV2.S/ Janssen	mRNA-1273/ Moderna	BNT162b2/ Pfizer
n	11,668	1870	348	778	443	65	153	83
Age	64 ± 14	64 ± 14	62 ± 13	64 ± 14	67 ± 13	65 ± 13	60 ± 12	64 ± 14
Male sex	6761 (58)	1087 (58)	190 (55)	471 (61)	255 (58)	35 (54)	83 (54)	53 (64)
Race								
Native American	319 (3)	145 (8)	6 (2)	50 (6)	55 (12)	1 (2)	21 (14)	12 (15)
Asian/Pacific Islander	413 (4)	105 (6)	7 (2)	35 (5)	49 (11)	0 (0)	6 (4)	8 (10)
Black	4397 (38)	438 (23)	170 (49)	118 (15)	81 (18)	31 (48)	20 (13)	18 (22)
Unknown/Other	1180 (10)	224 (12)	33 (10)	113 (15)	48 (11)	5 (8)	18 (12)	7 (8)
White	5359 (46)	958 (51)	132 (38)	462 (59)	210 (47)	28 (43)	88 (58)	38 (46)
Hispanic ethnicity	825 (7)	301 (16)	10 (3)	148 (19)	61 (14)	7 (11)	61 (40)	14 (17)
Vintage, months	35.0 [15.0, 69.7]	36.6 [15.5, 69.7]	38.5 [13.8, 81.7]	36.1 [16.4, 69.5]	33.9 [14.4, 61.9]	37.0 [17.1, 84.6]	39.4 [18.1, 60.5]	40.1 [17.9, 86.6]
Body mass index, kg/m^2	29.0 ± 7.5	28.5 ± 7.2	29.3 ± 8.0	28.2 ± 6.6	28.1 ± 7.3	29.7 ± 7.4	28.5 ± 8.1	27.9 ± 6.4
Diabetes	6873 (59)	1100 (59)	216 (62)	435 (56)	253 (57)	41 (63)	100 (65)	55 (66)
Long-term care facility	1816 (16)	275 (15)	37 (11)	91 (12)	48 (11)	21 (32)	39 (26)	39 (47)
Modality								
Home hemodialysis	131 (1)	38 (2)	1 (0.3)	26 (3)	10 (2)	0 (0)	1 (0.7)	0 (0)
In-center hemodialysis	10,155 (87)	1606 (86)	312 (90)	634 (82)	380 (86)	60 (92)	141 (92)	79 (95)
Peritoneal dialysis	1382 (12)	226 (12)	35 (10)	118 (15)	53 (12)	5 (8)	11 (7)	4 (5)
Inadequate dialysis [b]	1957 (17)	281 (15)	59 (17)	126 (16)	66 (15)	6 (9)	17 (11)	7 (8)
Albumin, g/dL	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.5	3.9 ± 0.4	3.9 ± 0.4	3.8 ± 0.4
HBsAb ≥10 mIU/mL [c]	8161 (70)	1435 (77)	252 (72)	606 (78)	332 (75)	48 (74)	134 (88)	63 (76)
History of transplantation	647 (6)	108 (6)	18 (5)	45 (6)	29 (7)	4 (6)	5 (3)	7 (8)
Immunodeficiency	459 (4)	84 (5)	19 (6)	32 (4)	24 (5)	3 (5)	5 (3)	1 (1)
Immunomodulating medication [d]	1627 (14)	243 (13)	44 (13)	92 (12)	71 (16)	8 (12)	18 (12)	10 (12)
Congestive heart failure	2306 (20)	329 (18)	75 (22)	139 (18)	69 (16)	11 (17)	20 (13)	15 (18)
Peripheral vascular disease	1396 (12)	188 (10)	56 (16)	65 (8)	36 (8)	12 (19)	11 (7)	8 (10)
Cerebrovascular disease	983 (8)	131 (7)	30 (9)	50 (6)	30 (7)	9 (14)	6 (4)	6 (7)
Chronic obstructive pulmonary disease	1623 (14)	240 (13)	64 (18)	92 (12)	54 (12)	10 (15)	11 (7)	9 (11)
History of cancer	1032 (9)	174 (9)	22 (6)	74 (10)	49 (11)	5 (8)	17 (11)	7 (8)
Duration of follow-up, days	---	158 [125, 187]	133 [110, 168]	159 [132, 187]	169 [134, 192]	176 [170, 198]	151 [124, 187]	178 [143, 202]

Vintage and duration of follow-up are reported as median [IQR]. All other data are reported as mean ± standard deviation or %. Data on baseline patient characteristics were complete.

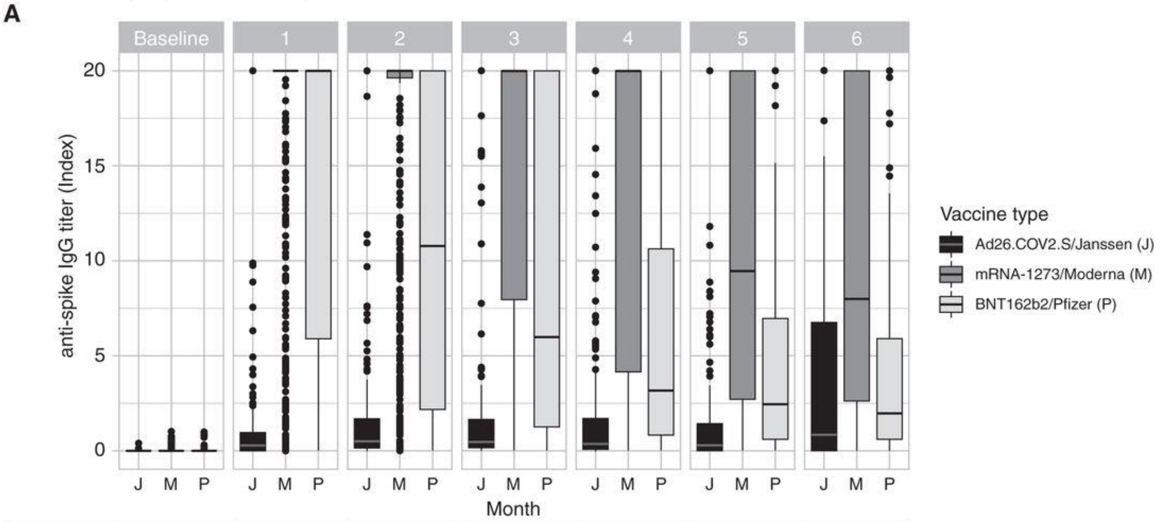
[a] Patients fully vaccinated with an emergency-use approved vaccine series of one type without additional doses before August 13, 2021

[b] Inadequate dialysis defined by hemodialysis dose spKt/V<1.2 or peritoneal dialysis dose weekly Kt/V<1.7

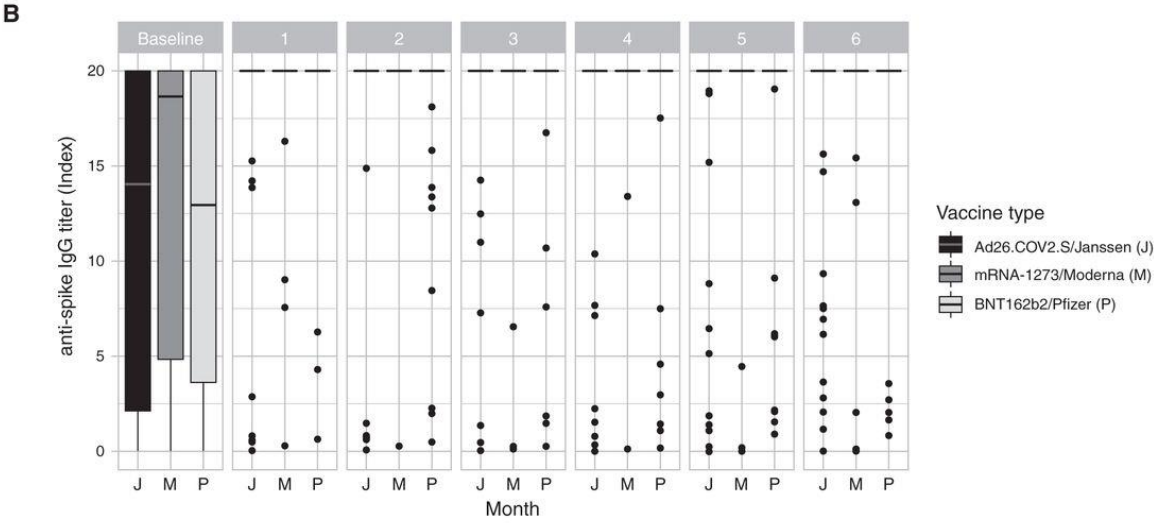
[c] HBsAb ≥10 mIU/mL signifies hepatitis B seroimmunity

[d] Immunomodulating medications include anti-inflammatory medications, anti-neoplastic agents, corticosteroids, and certain anti-infective medications

Figure 5.2. Anti-spike IgG titers versus months after date of full immunization, comparing by vaccine type.



N =	Baseline	1	2	3	4	5	6
Ad26/COV2.S/ Janssen	41	297	321	312	315	286	182
mRNA-1273/ Moderna	411	645	719	706	649	591	439
BNT162b2/ Pfizer	208	340	407	401	379	340	244



N =	Baseline	1	2	3	4	5	6
Ad26/COV2.S/ Janssen	19	54	58	57	56	58	56
mRNA-1273/ Moderna	99	118	142	140	128	113	74
BNT162b2/ Pfizer	45	72	74	74	73	66	52

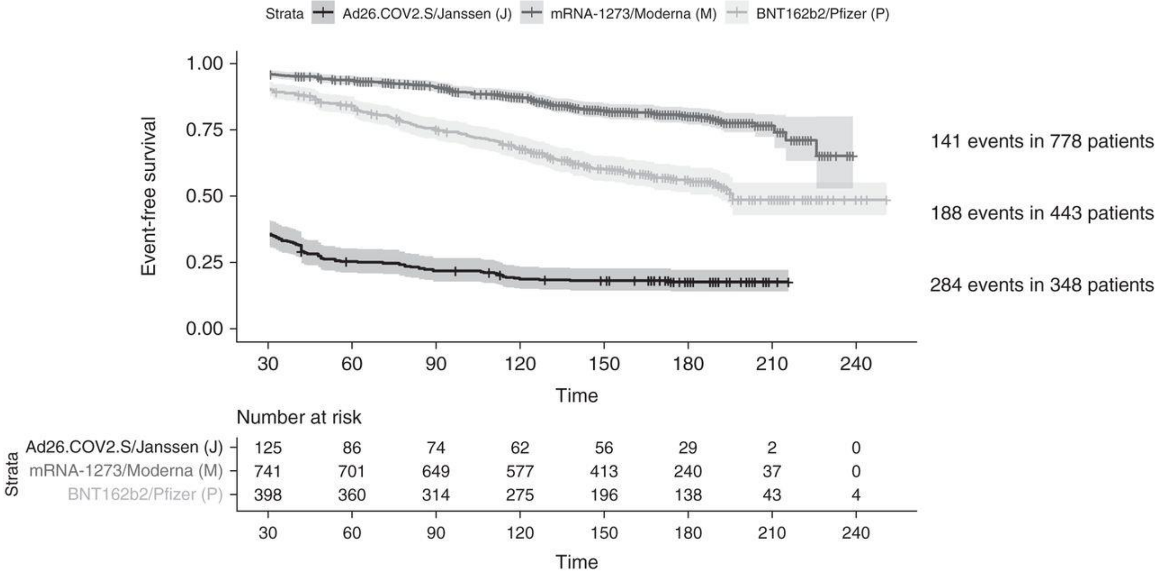
(A) Among patients without prior COVID-19, anti-spike IgG titers waned over time. (B) Among patients with prior COVID-19, anti-spike IgG titers remained stable. Of note, the box plots shown here are bounded by the upper and lower limits of the assay used. For example, in (A), the median (interquartile range; IQR) titer in month 1 was ≥20 (≥20 to ≥20) among the recipients of mRNA-1273 and ≥20 (5.89 to ≥20) among recipients of BNT162b2. The dots represent the outliers, defined as >1.5×IQR above the third quartile or <1.5×IQR below the first quartile. The tables below the plots show the number of titers for each month, by vaccine type.

mRNA-1273/Moderna, median [IQR, N number of data values] anti-spike IgG titer declined from ≥20 [≥20, ≥20; N of 645] in month 1 to ≥20 [4.14, ≥20; N of 649] by month 4 and to 7.99 [2.61, ≥20; N of 439] by month 6. Over all time periods, recipients of Ad26.COV2.S/Janssen had median anti-spike IgG titers of less than 1 Index, without a significant change over time. Among patients with a history of COVID-19, >75% maintained antibody titer at the upper limit of the assay's detection (≥20 Index) through month 6 (Figure 5.2B).

Among the 1569 patients without a history of COVID-19, 613 developed anti-spike IgG titer < 1 Index or were diagnosed with COVID-19 (589 and 24 patients, respectively). Time-to-event analysis showed a difference by vaccine type, with recipients of Ad26COV2.S/Janssen having the shortest time to anti-spike IgG < 1 Index, whereas recipients of mRNA-1273/Moderna recipients had more durable anti-spike IgG titer levels (Figure 5.3). At month 4, 67% of Janssen, 29% of Pfizer, and 11% of Moderna recipients had anti-spike titers <1 Index; at month 6, 52% of Janssen, 33% of Pfizer, and 10% of Moderna recipients had anti-spike IgG of <1 Index. Sensitivity analysis using the threshold of anti-spike IgG titer <2 Index instead showed more events occurring, as expected, but the differences by vaccine type remained (Supplemental Figure S5.1). Results changed minimally in sensitivity analysis using the outcome of anti-spike IgG titer <1 alone (Supplemental Figure S5.2).

To assess whether initial seroresponse is associated with sustained response, patients were then grouped by maximum titer measured during the first two months after full

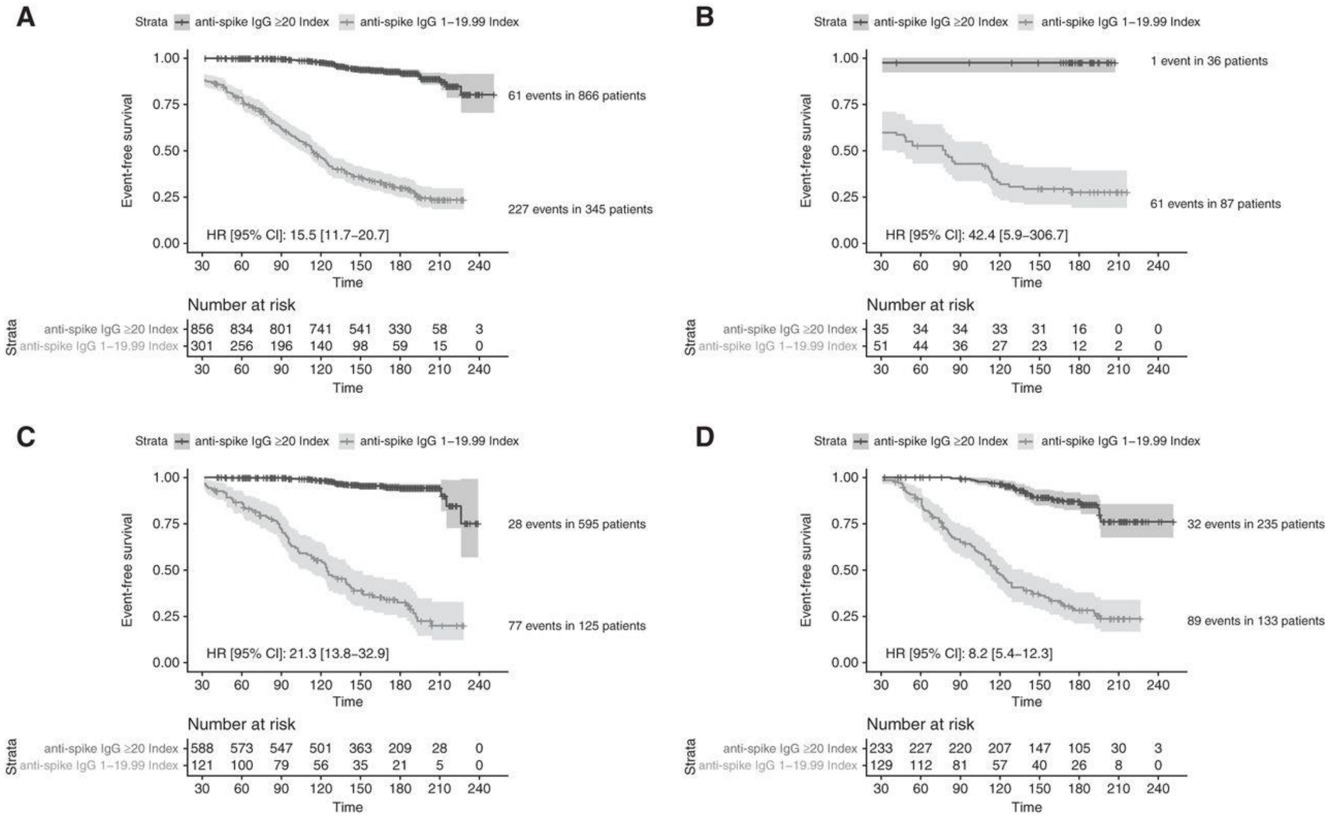
Figure 5.3. Kaplan–Meier time-to-event curves for the outcome of antibody titer <1 Index or diagnosis of COVID-19, among those without a history of COVID-19, by vaccine type.



Among patients without prior COVID-19, Ad26COV2.S/Janssen recipients had the shortest time to anti-spike IgG <1 Index, and mRNA-1273/Moderna recipients had more durable anti-spike IgG titer levels. Data are shown beginning at day 30, at which time all patients have had at least one opportunity for assessment of the outcome of antibody titer <1 Index *via* monthly laboratory measures. The curves, therefore, start at the proportion of patients who had not experienced the outcome as of day 30. Patients were censored at death, transplantation, administration of an additional vaccine dose (third dose or booster dose), or last available titer assessment.

vaccination: 866, 345, and 302 patients had maximum initial titer of ≥20, 1 to <20, and less than 1 Index, respectively, whereas 56 patients did not have a titer assessed during the first two months of full immunity and were excluded from this analysis. Baseline characteristics by maximum initial titer are shown in Supplemental Table S5.1. In time-to-event analysis, those who had a maximum initial titer ≥20 Index were less likely to develop the outcome of titer <1 Index or COVID-19 compared with those with a maximum initial titer from 1 to 19.99 Index. This difference persisted even among recipients of the same vaccine type (Figures 5.4A-D), in sensitivity analyses for the outcome of titer <2 Index (with corresponding change in strata thresholds, Supplemental Figures S5.3A-D), and in sensitivity analyses for the outcome of titer <1 Index alone

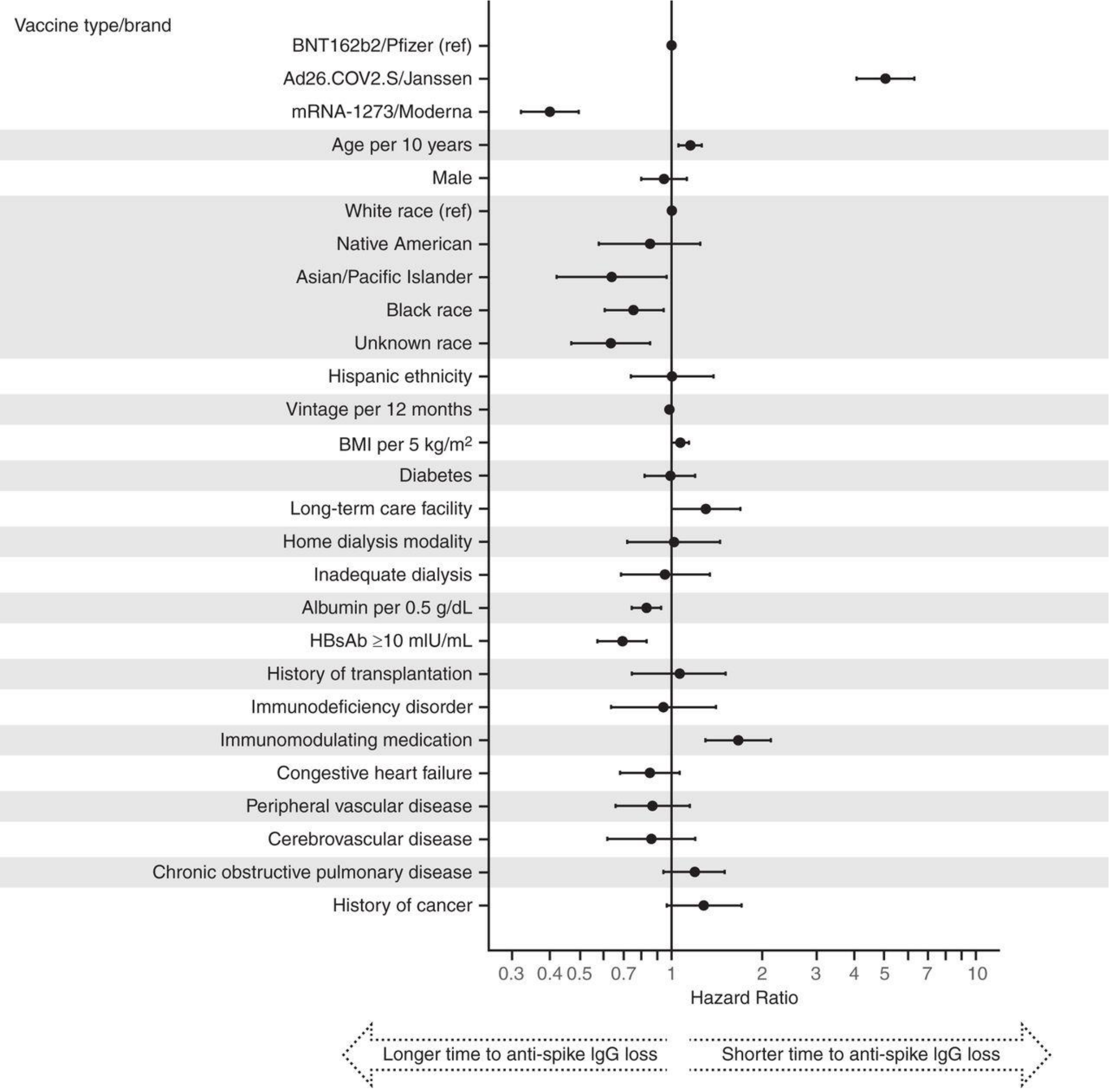
Figure 5.4. Kaplan–Meier time-to-event curves for the outcome of anti-spike IgG titer <1 Index or diagnosis of COVID-19, among those without a history of COVID-19, by maximum initial anti-spike IgG titer.



Among patients without prior COVID-19, those with higher maximum initial anti-spike IgG titer had more durable anti-spike IgG titer levels. Data are shown beginning at day 30, at which time all patients have had at least one opportunity for assessment of the outcome of anti-spike IgG titer <1 Index via monthly laboratory measures. The curves, therefore, start at the proportion of patients who had not experienced the outcome as of day 30. Patients were censored at death, transplantation, administration of an additional vaccine dose (third dose or booster dose), or last available titer assessment. Patients with maximum initial anti-spike IgG titer <1 Index are not shown because, given our definition of maximum initial titer, all had experienced the outcome by the end of month 2. (A) All patients; (B) recipients of Ad26.COV2.S only; (C) recipients of mRNA-1273 only; (D) recipients of BNT162b2 only. 95% CI, 95% confidence interval; HR, hazard ratio.

(Supplemental Figures S5.4A-D). In multivariable Cox proportional hazards regression, in addition to differences by vaccine type, older age, White race, higher body mass index, lower albumin, lack of hepatitis B seroimmunity, and use of immunomodulating

Figure 5.5 In multivariable Cox proportional hazards regression, vaccine type was most strongly associated with loss of anti-spike IgG seroresponse (outcome of anti-spike IgG titer <1 Index or development of COVID-19).



Inadequate dialysis defined by hemodialysis dose single-pool Kt/V <1.2 or peritoneal dialysis dose weekly Kt/V <1.7. Hepatitis B surface antibody (HBsAb) ≥10 mIU/ml signifies hepatitis B seroimmunity. Immunomodulating medications include anti-inflammatory medications, antineoplastic agents, corticosteroids, and certain anti-infective medications. BMI, body mass index; ref, reference.

medications were associated with shorter time to loss of seroresponse (Figure 5.5). In sensitivity analysis using the outcome of titer < 2 Index, body mass index was no longer associated with loss of seroresponse; other findings were similar (Supplemental Figure S5.5). Results were minimally changed in sensitivity analysis using the outcome of titer <1 Index alone (Supplemental Figure S5.6).

5.4 Discussion

Among a national population of patients receiving maintenance dialysis, mRNA vaccines elicited greater seroresponse than the Ad26.COV2.S/Janssen vaccine, but antibody titers against the SARS-CoV-2 spike protein waned substantially over the first six months after full vaccination among patients without a prior history of COVID-19. Furthermore, the robustness of the initial antibody response is associated with the rapidity of subsequent waning of antibody levels. Other clinical factors associated with the duration of seroresponse largely reflect patients' immune health.

As of December 2021, the CDC has issued recommendations for booster doses of SARS-CoV-2 vaccine, prompted by concerns about the durability of vaccine response.[97] In particular, patients receiving maintenance dialysis have had an attenuated response to other vaccines[31] and are at high risk for poor outcomes during the COVID-19 pandemic.[64] Critically, initial studies suggest that vaccine-induced immunity among maintenance dialysis patients immediately after receipt of a vaccine series was intermediate, with somewhat lesser response than among the general population but a greater response than among patients receiving immunosuppression for transplantation or other indications.[98–105] Our data provide longitudinal evidence of immunity waning fairly rapidly over time, with about half of maintenance dialysis patients developing undetectable antibody protection at six months after full vaccination. Data from both the initial vaccine trials and more recent real-world observation studies show some waning of anti-spike IgG titers over time in healthy adults, although the magnitude of the decline has varied greatly between studies.[112–118] Although the antibody level needed for protection from disease has not been definitively determined, a general correlation between seroimmunity and protection from disease has been observed.[119] Additionally, individuals with seroimmunity may be less likely to transmit the virus, providing protection to other vulnerable patients in mandatory congregate healthcare settings (O. Prunas *et al*., unpublished data).[120] Similar data on waning immunity prompted officials in France to recommend an additional vaccine dose to patients on maintenance dialysis in April 2021, with some early evidence of subsequent strengthened immunity in several small studies.[111,121–123]

There may be a role for wider routine monitoring of anti-spike IgG titers for patients on maintenance dialysis. Seroimmunity to hepatitis B is currently monitored through such a protocol, and, due to this population's regular and frequent contact with the medical system, routine testing and administration of additional doses would not be logistically difficult. In particular, the peak response in the first two months of full immunity indicates the patient's likely course and could be used to anticipate the timing of loss of seroimmunity.[115] Of note, the CDC currently does not recommend using COVID-19 antibody testing to guide clinical decision-making.[124]

The apparent association of Black race with greater durability of seroresponse in this study may partially reflect the multivariable model's simultaneous adjustment for vaccine type, given that a disproportionately large fraction of recipients of Ad26.COV2.S/Janssen were of Black race. However, this association persisted when the analyses were restricted to only recipients of an mRNA vaccine. This association has been also observed in our prior work[125] and requires further investigation.

This study represents a real-world, geographically diverse, multi-center population of patients receiving maintenance dialysis in the United States, in whom prior risk of COVID-19 morbidity and mortality has been documented.[64,86] We acknowledge this study's limitations. The antibody monitoring protocol was more widely used by clinics with earlier vaccine administration, reflecting the early uncertainty around the vaccine's effectiveness among patients on maintenance dialysis. This clinic clustering use of the protocol may have induced a selection bias, although it is ameliorated by the bias occurring at the level of the clinics rather than the individual patient. As with all observational studies, confounding variables may affect interpretation of results. In particular, data for months 5 and 6 primarily reflect patients who received their doses vaccine early (e.g. January through March of 2021) with a moderately higher proportion of mRNA vaccine recipients, and these patients may be frailer at baseline. Patients without a baseline titer assessment may have been misclassified with respect to their COVID-19 history. We further acknowledge that missing data may have biased results. In addition, we did not correlate antibody titers with breakthrough infection, an issue that remains complex and controversial.

In conclusion, immunity to SARS-CoV-2 vaccines, as indicated by anti-spike IgG titers, wanes over time among patients on maintenance dialysis without a prior history of COVID-19. In the setting of SARS-CoV-2 variants of concern, the effect of waning titers on breakthrough infections needs to be monitored closely. The current CDC recommendation to provide a third vaccine dose on the basis of clinical assessment for immunocompromise is an important consideration for the maintenance dialysis population. A large proportion of patients receiving maintenance dialysis have suboptimal response to the currently recommended vaccine regimens. Therefore, additional doses of vaccine should be considered for this vulnerable population, whether routinely or, with further investigation, potentially guided by protective correlates, such as antibody response.

Chapter 6: Discussion

Throughout the COVID-19 pandemic, patients receiving dialysis have encountered a particular set of risks and challenges. Patients with COVID-19-associated acute kidney injury treated with dialysis have high rates of mortality, likely because AKI-KRT often reflects severe underlying illness.[10–15] Patients receiving maintenance dialysis for ESKD typically have high comorbid burden and may have uremia-associated immune compromise.[17–20] The vast majority are obligated to congregate three times a week for life-sustaining treatment in the form of in-center hemodialysis, and many rely on outside transportation and/or have additional frequent contact with the health care system due to other comorbidities.[126] Such limited ability to physically distance increases the risk of developing this highly transmissible infectious illness. When vaccines first became widely available, there was concern that they would be less effective among patients receiving dialysis, given prior experience with hepatitis B vaccines.[31] Our work sought to characterize these risks and challenges that are particular to dialysis patients throughout the multiple phases of the COVID-19 pandemic.

In the first surge, in spring 2020, patients who were critically ill with COVID-19 had high rates of acute kidney injury. The work presented in Chapter 2 found that, among those requiring dialysis for AKI, lower baseline kidney function and oliguria at the time of KRT initiation were associated with kidney nonrecovery; this suggests that recovery from acute kidney injury depends on both the baseline kidney function and the severity of the injury itself. Chronic dialysis has long-term implications both for patient's physical health and for their quality of life;[33–35] therefore, accurate prognostication of kidney outcomes may have implications for patient care beyond the COVID-19 pandemic.

Moreover, during the first phase of the pandemic, patients receiving maintenance dialysis were at higher risk for developing COVID-19, and among those with COVID-19, 90-day mortality approached 25% (Chapter 3). This phase of the pandemic threw a spotlight on health disparities; for many people, the ability to physically distance, through low household density, working from home, or accepting a loss of income, was a privilege and was more often available to affluent communities. In contrast, the pandemic more easily took hold in urban areas of high density; such communities tend to have a greater non-White population and, due to other social determinants of health, also tend to have higher prevalence of medical comorbid conditions.[67] Our work found that non-White race, more comorbid conditions, and treatment at an urban dialysis facility were associated with worse outcomes, highlighting this complex tangle of factors.

During the latter half of 2020, as characteristics of the pandemic shifted, increased testing capacity enabled diagnosis of asymptomatic and mildly symptomatic cases of COVID-19, and the pandemic shifted to include rural parts of the country.[24–26] Our analysis in Chapter 4 showed that, while patients receiving in-center dialysis had higher risk for COVID-19 than their home dialysis counterparts during the first phase of the pandemic, COVID-19 incidence had far greater parity during this second phase, suggesting that the measures that dialysis centers implemented, such as infection control and patient education, were effective in reducing the spread of disease. Of note, residence in a long-term care facility (LTCF) increased risk of COVID-19 more than 8-fold during the first phase of the pandemic but was not a significant risk factor in the second phase, suggesting that LTCFs were likewise implementing effective infection control measures.

Lastly, following the rollout of SARS-CoV-2 vaccines, we found that patients receiving maintenance dialysis typically mount an appropriate initial immune response; however, this immune response wanes relatively quickly (Chapter 5). Given their high risk for poor outcomes, patients receiving maintenance dialysis may therefore benefit from additional vaccine doses. Moreover, we found that the robustness of the early seroresponse was associated with the durability of the antibody titers. Therefore, serial antibody testing may have a role in helping guide timing of additional doses. Though the CDC does not generally recommend this approach at this time, such a protocol already exists for monitoring hepatitis B seroimmunity among patients receiving maintenance dialysis,[31] so a similar protocol for SARS-CoV-2 seroimmunity could be developed.

Altogether, the research presented here demonstrates that dialysis patients have a particular set of challenges in the COVID-19 pandemic. Throughout the pandemic, members of our research team have worked closely with such stakeholders as the CDC, the Reagan-Udall Foundation for the FDA, the American Society of Nephrology's Chief Medical Officer Group and COVID-19 Response Team, and the Nonprofit Kidney Care Alliance. Since January 2021, we have been posting our findings on the medRxiv preprint server. These efforts to engage the nephrology community and public health officials have enabled rapid dissemination of our work, thus affecting clinical decision-making in real-time.

At this time, further work is needed to characterize the seroresponse to third doses of vaccine and to establish the correlation between seroresponse and clinical outcomes. The emergence of SARS-CoV-2 variants has prompted a need to re-characterize the epidemiology of COVID-19 among patients receiving maintenance dialysis. Patients with kidney disease are at increased risk for poor outcomes, and evidence from further investigation should continue to guide their care throughout the pandemic.

Chapter 7: Bibliography

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