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Characteristics and Outcomes of Individuals With Pre-existing Kidney Disease and COVID-19 Admitted to Intensive Care Units in the United States

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Rationale & Objective: Underlying kidney disease is an emerging risk factor for more severe coronavirus disease 2019 (COVID-19) illness. We examined the clinical courses of critically ill COVID-19 patients with and without pre-existing chronic kidney disease (CKD) and investigated the association between the degree of underlying kidney disease and in-hospital outcomes.

Study Design: Retrospective cohort study.

Settings & Participants: 4,264 critically ill patients with COVID-19 (143 patients with pre-existing kidney failure receiving maintenance dialysis; 521 patients with pre-existing non-dialysis-dependent CKD; and 3,600 patients without pre-existing CKD) admitted to intensive care units (ICUs) at 68 hospitals across the United States.

Predictor(s): Presence (vs absence) of pre-existing kidney disease.

Outcome(s): In-hospital mortality (primary); respiratory failure, shock, ventricular arrhythmia/cardiac arrest, thromboembolic events, major bleeds, and acute liver injury (secondary).

Analytical Approach: We used standardized differences to compare patient characteristics (values > 0.10 indicate a meaningful difference between groups) and multivariable-adjusted Fine

and Gray survival models to examine outcome associations.

Results: Dialysis patients had a shorter time from symptom onset to ICU admission compared to other groups (median of 4 [IQR, 2-9] days for maintenance dialysis patients; 7 [IQR, 3-10] days for non-dialysis-dependent CKD patients; and 7 [IQR, 4-10] days for patients without pre-existing CKD). More dialysis patients (25%) reported altered mental status than those with non-dialysis-dependent CKD (20%; standardized difference = 0.12) and those without pre-existing CKD (12%; standardized difference = 0.36). Half of dialysis and non-dialysis-dependent CKD patients died within 28 days of ICU admission versus 35% of patients without pre-existing CKD. Compared to patients without pre-existing CKD, dialysis patients had higher risk for 28-day in-hospital death (adjusted HR, 1.41 [95% CI, 1.09-1.81]), while patients with non-dialysis-dependent CKD had an intermediate risk (adjusted HR, 1.25 [95% CI, 1.08-1.44]).

Limitations: Potential residual confounding.

Conclusions: Findings highlight the high mortality of individuals with underlying kidney disease and severe COVID-19, underscoring the importance of identifying safe and effective COVID-19 therapies in this vulnerable population.

Visual Abstract online

Complete author and article information provided before references.

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Since its emergence in Wuhan, China, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has snowballed into a global pandemic, infecting more than 28 million people across the globe and killing more than

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900,000 as of mid-September 2020.¹ Emerging data suggests that individuals with underlying kidney dysfunction have worse COVID-19–related outcomes than those without kidney dysfunction.^{2–8} Similar outcome differences across patients with and without kidney dysfunction have been observed in other illness states (eg, general critical illness⁹ and influenza¹⁰) and may relate in part to innate immunity impairment, vascular dysfunction, and the heightened

inflammatory state that are characteristic of advanced chronic kidney disease (CKD).^{11–13}

As such, individuals with underlying CKD may be particularly vulnerable to COVID-19–related critical illness, marked by multi-system organ failure, thrombosis, and a heightened inflammatory response. COVID-19–related critical illness affects ~10% of patients hospitalized with COVID-19 and has an exceedingly high mortality rate.^{14–17} Data from the United States indicate that patients with critical COVID-19 illness complicated by acute kidney injury have worse outcomes than those without acute kidney injury.^{18–21} Single-center and regional studies suggest that similarly poor outcomes occur among individuals with critical COVID-19 illness and pre-existing CKD, especially in patients with kidney failure receiving maintenance

PLAIN-LANGUAGE SUMMARY

Individuals with underlying kidney disease may be particularly vulnerable to severe coronavirus disease 2019 (COVID-19) illness, marked by multisystem organ failure, thrombosis, and a heightened inflammatory response. Among 4,264 critically ill adults with COVID-19 admitted to 68 intensive care units across the United States, we found that both non-dialysis-dependent chronic kidney disease patients and maintenance dialysis patients had a 28-day in-hospital mortality rate of ~50%. Patients with underlying kidney disease had higher in-hospital mortality than patients without pre-existing kidney disease, with patients receiving maintenance dialysis having the highest risk. As evidenced by differences in symptoms and clinical trajectories, patients with pre-existing kidney disease may have unique susceptibility to COVID-19-related complications, which warrants additional study and special consideration in the pursuit and development of targeted therapies.

dialysis, but study sample sizes were limited and most lacked comparator populations.²⁰⁻²⁵ Given the rapidly changing landscape of COVID-19 therapeutics and the potential for reduced kidney function to limit therapeutic options (eg, remdesivir), granular and broadly representative data characterizing the clinical courses of critically ill patients with COVID-19 and pre-existing CKD are needed to inform the management of this vulnerable population.

To address this knowledge gap, we used data from the Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19 (STOP-COVID), a cohort study of more than 4,000 patients with COVID-19 admitted to intensive care units (ICUs) at 68 hospitals across the United States and examined the clinical courses of critically ill COVID-19 patients with and without pre-existing CKD. We also investigated the association between degree of underlying kidney disease and occurrence of in-hospital mortality and other outcomes (eg, respiratory failure, shock, and thromboembolic events).

Methods

Patient Population and Study Design

We used data from STOP-COVID, a multicenter cohort study that enrolled consecutive adults (aged ≥ 18 years) with laboratory-confirmed COVID-19 admitted to ICUs at 68 geographically diverse US hospitals (Item S1). Cohort compilation and initial results have been previously reported.²⁶ The STOP-COVID parent study was approved by the institutional review boards at each participating site. This ancillary study was approved by the University of

North Carolina at Chapel Hill Institutional Review Board (#20-1395). A waiver of informed consent was granted due to the anonymity of the STOP-COVID limited data set used for this project.

In this ancillary study, focused on pre-existing kidney disease, we included 4,264 critically ill COVID-19 patients with and without pre-existing CKD admitted to 68 ICUs in the United States between March 4, 2020 and May 10, 2020. Using a retrospective cohort study design, we followed patients forward in historical time from ICU admission to in-hospital death, hospital discharge, or June 6, 2020, the date of database locking for these analyses. All patients still hospitalized at the time of data analysis had at least 28 days of follow-up. We excluded patients without documented vital signs on ICU day 1 ($n = 5$).

Data Collection

Study personnel at each STOP-COVID site collected data by detailed medical chart review and used a standardized electronic case report form to enter data into a secure Research Electronic Data Capture (REDCap) database. Abstracted data included demographics, comorbid conditions, and home medications; symptoms and vital signs at ICU admission; longitudinal laboratory and physiologic parameters, therapeutic interventions, and acute organ injury and support during the first 14 days after ICU admission; and dates and contributing causes of in-hospital death. For individuals with pre-existing kidney failure receiving maintenance dialysis, we also collected data on dialysis modality, dialysis vintage, and vascular access type (for hemodialysis patients), all preceding hospital admission.

Exposures

The exposures of interest were the presence of pre-existing non-dialysis-dependent CKD and kidney failure requiring maintenance dialysis. We defined pre-existing non-dialysis-dependent CKD as a baseline estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (based on either the Modification of Diet in Renal Disease [MDRD] Study²⁷ or CKD Epidemiology Collaboration [CKD-EPI]²⁸ equations) prior to hospitalization on at least 2 consecutive occasions at least 12 weeks apart or, in cases where pre-hospitalization eGFRs were unavailable, the presence of non-dialysis-dependent CKD in the medical chart problem list or past medical history. Individuals with prior kidney transplant were classified according to their baseline eGFR. We defined pre-existing kidney failure requiring maintenance dialysis as medical chart-documented maintenance dialysis therapy prior to hospital admission. We categorized patients without evidence of CKD or maintenance dialysis therapy as having no pre-existing CKD, and these individuals served as our referent group.

Outcomes

Primary outcomes were 14- and 28-day in-hospital mortality. Secondary outcomes included 14-day in-hospital respiratory failure, shock, ventricular arrhythmia or cardiac arrest, thromboembolic events (including ischemic stroke, pulmonary embolism, or deep vein thrombosis), major bleeds, and acute liver injury (Table S1).

Statistical Analysis

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). We described patient characteristics on ICU day 1, therapies administered, and laboratory parameters across exposure groups as count (percentage) for categorical variables and as median [interquartile range (IQR)] for continuous variables. We compared baseline covariate distributions using absolute standardized mean differences (ASMDs). An ASMD > 0.10 represents an imbalance (i.e., difference) between exposure groups.^{29,30} A larger ASMD is indicative of a larger between-group difference.

We assessed the association between the presence of pre-existing kidney disease (non-dialysis-dependent CKD and kidney failure requiring maintenance dialysis, separately) versus no pre-existing CKD and 14- and 28-day in-hospital mortality using Fine and Gray proportional subdistribution hazards models. Individuals were followed forward in historical time from ICU admission to the first occurrence of an outcome, censoring event (completion of 14 and 28 days of follow-up), or competing event (hospital discharge). Pre-specified subgroup analyses evaluated the association between vascular access type before hospital admission and dialysis vintage (separately) and mortality in hemodialysis patients, and baseline serum creatinine level (pre-hospital serum creatinine <1.2, 1.2-1.9, and ≥2.0 mg/dL) and mortality in patients with non-dialysis-dependent CKD.

We used similar methods to examine the association between the presence (vs absence) of pre-existing CKD and the occurrence of select secondary outcomes during the 14 days after ICU admission. We restricted these secondary analyses to individuals who were alive and free of the outcome of interest on ICU day 1. Follow-up began on ICU day 2, with both in-hospital death and hospital discharge treated as competing events. We adjusted associative models for demographics (model 1) and separately for demographics and comorbid conditions (model 2) when the number of outcome events was sufficient. Model 1 assesses the association of outcomes and underlying kidney disease overall, whereas model 2 assesses the association of outcomes and underlying kidney disease independent of comorbid conditions known to associate with COVID-19 outcomes.^{17,21,31-35} Using analogous methods, we performed separate sensitivity analyses excluding patients receiving therapeutic-level anti-coagulation on ICU day 1 from models examining major

bleeds and thromboembolic events, and excluding patients with a history of liver disease from models examining acute liver injury.

Results

Patient Characteristics

A total of 4,264 individuals with COVID-19 critical illness were included in the study: 143 (3%) with pre-existing kidney failure receiving maintenance dialysis, 521 (12%) with pre-existing non-dialysis-dependent CKD, and 3,600 (85%) without pre-existing CKD. Tables 1 and S2 to S4 display the demographic and clinical characteristics on ICU day 1 across study groups. Most (58%) patients in the study were cared for in ICUs located in the northeastern United States. Non-dialysis-dependent CKD patients were older than dialysis patients (median ages of 69 [IQR, 60-76] and 65 [IQR, 56-71] years, respectively; ASMD = 0.31) and patients without pre-existing CKD (median age of 61 [IQR, 51-70] years; ASMD = 0.55). Comorbid conditions including diabetes and cardiovascular conditions were more common in patients with pre-existing CKD (both maintenance dialysis and non-dialysis-dependent CKD patients) compared to those without CKD.

Of the 143 maintenance dialysis patients, 128 (90%) received in-center hemodialysis, 9 (6%) received peritoneal dialysis, 2 (1%) received home hemodialysis, and 4 (3%) had an undocumented modality before hospital admission. Of the 128 hemodialysis patients with a known vascular access type, 82 (64%), 35 (27%), and 11 (9%) dialyzed via a fistula, catheter, and graft, respectively, prior to admission.

The median time from COVID-19-related symptom onset to ICU admission was 4 (IQR, 2-9) days among maintenance dialysis patients, 7 (IQR, 3-10) days among non-dialysis-dependent CKD patients, and 7 (IQR, 4-10) days among patients without pre-existing CKD. In general, dialysis patients reported COVID-19-related symptoms before ICU admission at a lower frequency than patients without CKD, with 1 exception: the percentage of dialysis patients reporting altered mental status was more than twice that of patients without CKD (25% vs 12%; ASMD = 0.36) and slightly more than that of patients with non-dialysis-dependent CKD (25% vs 20%; ASMD = 0.12). In addition, respiratory symptoms were less frequent in dialysis patients compared to the other groups.

Tables 2 and S2 to S4 display COVID-19 severity and laboratory findings on ICU day 1 across study groups. A modestly higher percentage of patients without pre-existing CKD (63%) required invasive mechanical ventilation on ICU day 1 compared to maintenance dialysis patients (56%; ASMD = 0.15). Median white blood cell counts, platelet counts, and fibrinogen concentrations on ICU day 1 were lower in dialysis patients compared to patients without pre-existing CKD, whereas median C-reactive protein,

Table 1. Characteristics of Critically Ill COVID-19 Patients on ICU Day 1

Characteristic ^a	Maintenance Dialysis Patients (n = 143)	Patients With Non-Dialysis-Dependent CKD (n = 521)	Patients Without Pre-existing CKD (n = 3,600)
Demographics			
Age, y	65 [56-71]	69 [60-76]	61 [51-70]
Male sex	77 (54%)	323 (62%)	2,314 (64%)
Race^a			
White	48 (34%)	184 (35%)	1,403 (39%)
Black	71 (50%)	232 (45%)	963 (27%)
Other race	5 (3%)	34 (7%)	309 (9%)
Unknown/not reported	19 (13%)	71 (14%)	925 (26%)
Ethnicity^a			
Hispanic	29 (20%)	66 (13%)	919 (26%)
Non-Hispanic	107 (75%)	411 (79%)	2,218 (62%)
Unknown/not reported	7 (5%)	44 (8%)	463 (13%)
BMI, kg/m ²	28.3 [23.8-34.7]	30.3 [26.3-36.3]	30.4 [26.5-35.6]
US geographic region			
Northeast	78 (55%)	241 (46%)	2,175 (60%)
South	27 (19%)	65 (12%)	388 (11%)
Midwest	31 (22%)	169 (32%)	717 (20%)
West	7 (5%)	46 (9%)	320 (9%)
Comorbid conditions			
Diabetes	97 (68%)	329 (63%)	1,337 (37%)
Hypertension	125 (87%)	451 (87%)	2,036 (57%)
Coronary artery disease	55 (38%)	146 (28%)	374 (10%)
Heart failure	44 (31%)	136 (26%)	233 (6%)
Atrial fibrillation or flutter	31 (22%)	70 (13%)	211 (6%)
Asthma or COPD	21 (15%)	118 (23%)	617 (17%)
Chronic liver disease	7 (5%)	33 (6%)	103 (3%)
Home medications			
ACEi or ARB	35 (24%)	243 (47%)	1,127 (31%)
β-Blocker	98 (69%)	264 (51%)	768 (21%)
Other antihypertensive	69 (48%)	296 (57%)	937 (26%)
Statin	80 (56%)	317 (61%)	1,226 (34%)
Aspirin	65 (45%)	213 (41%)	668 (19%)
Anticoagulant	38 (27%)	95 (18%)	294 (8%)
NSAID	3 (2%)	26 (5%)	322 (9%)
ICU admission source			
Emergency department	82 (57%)	299 (57%)	1,981 (55%)
Hospital ward	47 (33%)	165 (32%)	1,114 (31%)
Transfer from another hospital	12 (8%)	50 (10%)	487 (14%)
Other	2 (1%)	6 (1%)	18 (1%)
Days from symptom onset to ICU admission	4 [2-9]	7 [3-10]	7 [4-10]
Symptoms			
Shortness of breath	85 (59%)	360 (69%)	2,733 (76%)
Cough	81 (57%)	322 (62%)	2,698 (75%)
Fever	82 (57%)	294 (56%)	2,486 (69%)
Altered mental status	36 (25%)	106 (20%)	418 (12%)
Myalgia or arthralgia	15 (10%)	94 (18%)	815 (23%)
Headache	4 (3%)	27 (5%)	343 (10%)
Nausea or vomiting	27 (19%)	60 (12%)	573 (16%)
Diarrhea	26 (18%)	115 (22%)	708 (20%)

Note: Values are given as number (percent) for categorical variables and as median [interquartile range] for continuous variables. Absolute standardized mean differences comparing the patient groups with one another are presented in Tables S2 to S4. Variables with missing values are presented in Table S13.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug.

^aInformation on race and ethnicity were abstracted from the electronic health record of each patient. In the United States, people of Hispanic ethnicity are those of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race.

Table 2. Illness Severity and Laboratory Findings of Critically Ill COVID-19 Patients on ICU Day 1

Characteristic	Maintenance Dialysis Patients (n = 143)	Patients With Non-Dialysis-Dependent CKD (n = 521)	Patients Without Pre-existing CKD (n = 3,600)
Vital signs			
Highest temperature, °C	37.8 [37.1-38.5]	37.7 [37.1-38.4]	38.0 [37.2-38.9]
Fever: >38°C	65 (45%)	213 (41%)	1,837 (51%)
Lowest systolic BP, mm Hg	92 [81-108]	96 [84-112]	97 [85-110]
Highest heart rate, beats/min	101 [88-119]	101 [87-116]	105 [92-121]
Highest respiratory rate, breaths/min	29 [23-35]	30 [26-36]	32 [26-38]
Severity of illness markers			
Invasive mechanical ventilation	80 (56%)	311 (60%)	2,284 (63%)
PEEP, cm H ₂ O	10 [8-14]	10 [10-15]	12 [10-15]
Pao ₂ :Fio ₂ ratio, mm Hg	164 [101-267]	125 [79-190]	122 [83-191]
Noninvasive mechanical ventilation	3 (2%)	16 (3%)	86 (2%)
High-flow nasal cannula or nonrebreather mask	29 (20%)	121 (23%)	801 (22%)
AKI requiring dialysis	—	27 (5%)	55 (2%)
Renal SOFA score^a			
0 (creatinine < 1.2 mg/dL)	0 (0%)	62 (12%)	2,347 (65%)
1 (creatinine 1.2-1.9 mg/dL)	0 (0%)	168 (32%)	844 (23%)
2 (creatinine 2.0-3.4 mg/dL)	0 (0%)	143 (27%)	255 (7%)
3 (creatinine 3.5-4.9 mg/dL)	0 (0%)	68 (13%)	71 (2%)
4 (creatinine ≥ 5.0 mg/dL or KRT)	143 (100%)	80 (15%)	83 (2%)
Liver SOFA score^b			
0 (bilirubin < 1.2 mg/dL)	132 (92%)	482 (93%)	3,253 (90%)
1 (bilirubin 1.2-1.9 mg/dL)	7 (5%)	28 (5%)	251 (7%)
≥ 2 (bilirubin ≥ 2.0 mg/dL)	4 (3%)	11 (2%)	96 (3%)
Coagulation SOFA score^c			
0 (platelet count ≥ 150 K/μL)	90 (63%)	408 (78%)	2,989 (83%)
1 (platelet count 100-149 K/μL)	37 (26%)	80 (15%)	467 (13%)
≥ 2 (platelet count < 100 K/μL)	16 (11%)	33 (6%)	144 (4%)
Vasopressor or inotrope use	72 (50%)	219 (42%)	1,482 (41%)
Shock ^d	17 (12%)	75 (14%)	370 (10%)
Coinfections			
Bacterial pneumonia	24 (17%)	85 (16%)	489 (14%)
Bacteremia or endocarditis	11 (8%)	16 (3%)	80 (2%)
Laboratory findings			
WBC count, ×10 ³ /μL	7.5 [5.7-10.4]	8.2 [5.8-11.6]	8.5 [6.1-11.9]
Lymphocyte count, ×10 ³ /μL	9.7 [5.4-15.1]	9.4 [5.7-14.9]	10.0 [6.0-15.1]
Hemoglobin, g/dL	10.3 [9.0-11.8]	11.4 [9.5-12.9]	12.8 [11.4-14.2]
Platelet count, ×10 ³ /μL	167 [124-212]	202 [155-258]	218 [167-281]
Serum creatinine, mg/dL	7.7 [5.6-10.1]	2.2 [1.5-3.6]	1.0 [0.8-1.4]
AST, U/L	46 [30-72]	48 [33-80]	54 [36-85]
ALT, U/L	23 [17-40]	28 [18-47]	38 [24-62]
Bilirubin, mg/dL	0.6 [0.4-0.7]	0.5 [0.3-0.8]	0.6 [0.4-0.8]
Lactate, mmol/L	1.6 [1.0-2.6]	1.6 [1.0-2.4]	1.6 [1.1-2.3]
CRP, mg/L	170.0 [73.0-277.7]	142.4 [84.8-217.5]	151.0 [81.6-235.7]
IL-6, pg/mL	121.4 [41.3-320.4]	52.0 [19.0-175.3]	56.0 [18.0-156.6]
Arterial pH	7.37 [7.28-7.43]	7.34 [7.26-7.40]	7.38 [7.30-7.44]
Fibrinogen, mg/dL	542 [369-619]	588 [442-732]	614 [491-764]

(Continued)

interleukin 6, ferritin, and troponin levels were higher in dialysis patients (all ASMDs > 0.10). Similar laboratory patterns were observed for platelet counts, fibrinogen

concentrations, and troponin levels when comparing patients with non-dialysis-dependent CKD to patients without pre-existing CKD, but the differences were of lower magnitudes.

Table 2 (Cont'd). Illness Severity and Laboratory Findings of Critically Ill COVID-19 Patients on ICU Day 1

Characteristic	Maintenance Dialysis Patients (n = 143)	Patients With Non-Dialysis-Dependent CKD (n = 521)	Patients Without Pre-existing CKD (n = 3,600)
D-Dimer, ng/mL	1,347 [609-2,623]	1,385 [670-3,018]	1,270 [652-3,459]
Ferritin, ng/mL	3,406 [1,795-6,271]	984 [450-1,981]	947 [489-1,919]
Troponin T, ng/mL	175 [95-364]	51 [25-110]	12 [4-40]
Troponin I, ng/mL	140 [70-330]	55 [20-170]	30 [10-110]

Note: Values are given as number (percent) for categorical variables and as median [interquartile range] for continuous variables. Absolute standardized mean differences comparing the patient groups to one another are presented in Tables S2 to S4. Variables with missing values are presented in Table S13.

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IL-6, interleukin 6; KRT, kidney replacement therapy; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

^aRenal component of the SOFA score was based on the serum creatinine level. Patients who did not have a serum creatinine drawn on ICU day 1 were classified as having renal SOFA score of 0, and patients on KRT were classified as having a renal SOFA score of 4.⁴⁹

^bLiver component of the SOFA score. Patients who did not have a serum bilirubin drawn on ICU day 1 were classified as having a liver SOFA score of 0.⁴⁹

^cCoagulation component of the SOFA score. Patients who did not have a platelet count drawn on ICU day 1 were classified as having a coagulation SOFA score of 0.⁴⁹

^dShock is defined as the requirement of 2 or more vasopressors or inotropes.

Targeted Therapies and Clinical Trajectories

Table 3 displays COVID-19–targeted therapies administered during the 14 days after ICU admission in each group (Table S5: corresponding ASMDs). Compared to maintenance

dialysis patients, a higher percentage of patients without pre-existing CKD were mechanically ventilated (74% vs 80%; ASMD = 0.15). Prone positioning was used in a higher percentage of patients without pre-existing CKD (42%)

Table 3. COVID-19 Targeted Therapies Administered During the First 14 Days After ICU Admission

Therapy	Maintenance Dialysis Patients (n = 143)	Patients With Non-Dialysis-Dependent CKD (n = 521)	Patients Without Pre-existing CKD (n = 3,600)
Anti-infective agent			
HCC or CQ ^a	83 (58%)	352 (68%)	2,487 (69%)
Azithromycin ^a	63 (44%)	274 (53%)	1,959 (54%)
HCC or CQ + azithromycin ^a	36 (25%)	127 (24%)	1,127 (31%)
Remdesivir	0 (0%)	13 (2%)	262 (7%)
Ribavirin	0 (0%)	2 (0%)	14 (0%)
Lopinavir/ritonavir	5 (3%)	15 (3%)	154 (4%)
Anti-inflammatory agent			
Any corticosteroid ^b	52 (36%)	204 (39%)	1,357 (38%)
Dexamethasone ^b	3 (2%)	11 (2%)	137 (4%)
NSAID	1 (1%)	10 (2%)	160 (4%)
Aspirin	54 (38%)	151 (29%)	596 (17%)
Statin	55 (38%)	182 (35%)	822 (23%)
Tocilizumab	13 (9%)	73 (14%)	667 (19%)
Vitamin C	10 (7%)	53 (10%)	371 (10%)
Respiratory and cardiac intervention			
Invasive mechanical ventilation	106 (74%)	404 (78%)	2,891 (80%)
Neuromuscular blockade	27 (19%)	163 (31%)	1,410 (39%)
Inhaled epoprostenol	1 (1%)	29 (6%)	185 (5%)
Inhaled nitric oxide	4 (3%)	19 (4%)	132 (4%)
Prone positioning	35 (24%)	142 (27%)	1,495 (42%)
ECMO	1 (1%)	3 (1%)	157 (4%)
Vasopressor or inotrope	106 (74%)	366 (70%)	2,502 (70%)
Mechanical cardiac support ^c	1 (1%)	1 (0%)	5 (0%)
Other			
Therapeutic anticoagulation ^d	64 (45%)	232 (45%)	1,656 (46%)
Convalescent serum	4 (3%)	10 (2%)	132 (4%)

Note: Values are given as number (percent) of patients. Absolute standardized mean differences comparing the patient groups to one another are presented in Table S5. Abbreviations: CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CQ, chloroquine; ECMO, extracorporeal membrane oxygenation; HCC, hydroxychloroquine; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug.

^aThe anti-infective medication categories of HCC or CQ, azithromycin, and HCC or CQ + azithromycin are not mutually exclusive.

^bThe anti-inflammatory agent categories of any corticosteroid and dexamethasone are not mutually exclusive.

^cMechanical cardiac support included an intra-aortic balloon pump, Impella heart pump (ABIOMED), and left and right ventricular assist devices.

^dTherapeutic anticoagulation included continuous drips of heparin, argatroban, or bivalirudin; subcutaneous enoxaparin (1.5 mg/kg once per day), dalteparin (150-200 U/kg once per day or 100 U/kg twice per day, fondaparinux (≥5 mg per day); and oral anticoagulants (eg, warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran).

compared to non-dialysis-dependent CKD (27%; ASMD = 0.30) and dialysis (24%; ASMD = 0.37) patients. Remdesivir was more commonly administered to patients without pre-existing CKD (7%) compared to non-dialysis-dependent CKD patients (2%; ASMD = 0.22). No maintenance dialysis patients received remdesivir. Patients without pre-existing CKD received tocilizumab (19%) more often than non-dialysis-dependent CKD (14%; ASMD = 0.12) and dialysis (9%; ASMD = 0.28) patients.

Figures 1 and S1 display laboratory parameter trajectories during the first 14 days after ICU admission across groups. In general, maintenance dialysis and non-dialysis-dependent CKD patients had lower platelet counts and higher C-reactive protein levels compared to patients without pre-existing CKD. Lactate levels on ICU day 1 were similar across groups, but elevated levels persisted longer in dialysis patients compared to the other groups. Longitudinally, ferritin and troponin levels were highest in dialysis patients and lowest in patients without pre-existing CKD.

In-Hospital Outcomes

Figure 2 depicts patient disposition at 14 and 28 days after ICU admission. The leading contributing cause of death across all patient groups was respiratory failure (Fig S2). Compared to no pre-existing CKD, non-dialysis-dependent CKD and kidney failure requiring maintenance dialysis were associated with higher risks of 14- and 28-day in-hospital mortality (Table 4). In models examining the association between in-hospital mortality and pre-existing kidney disease status, independent of other comorbid conditions (ie, models adjusted for demographic and comorbid conditions), the associations were slightly attenuated but remained statistically significant (fully adjusted hazard ratios [HRs] for 28-day in-hospital mortality of 1.25 [95% CI, 1.08-1.44] and 1.41 [95% CI, 1.09-1.81] for non-dialysis-dependent CKD and maintenance dialysis-dependent kidney failure, respectively). Models evaluating 14-day in-hospital mortality produced similar results. Of the patients who died during the 28 days following ICU admission, median times from ICU admission to death were 8 (IQR, 5-11), 8 (IQR, 5-13), and 10 (IQR, 6-16) days for the maintenance dialysis, non-dialysis-dependent CKD, and no pre-existing CKD groups, respectively. Mortality rates across exposure groups were stable during the study period (Table S6).

Figure 3 and Table S7 display secondary outcome associations across patient groups. Dialysis patients had nominally higher risks of shock, ventricular arrhythmia or cardiac arrest, major bleeding events, and acute liver injury during the 14 days after ICU admission, though these findings were not statistically significant. The occurrence of thromboembolic events was similar across patient groups. Sensitivity analyses excluding patients receiving therapeutic anticoagulation from major bleed and thromboembolic event models and excluding patients with a history of liver disease from acute liver injury models produced similar results (Tables S8 and S9).

Pre-existing Kidney Disease Subgroups

Tables S10 to S12 display results from all pre-existing kidney disease subgroup analyses. Of the 397 individuals with pre-existing non-dialysis-dependent CKD and known baseline serum creatinine levels, there was a nominally higher risk of in-hospital mortality with higher baseline serum creatinine concentrations, but results did not reach statistical significance. Among the 128 in-center hemodialysis patients, dialysis through a catheter (vs an arteriovenous access) was associated with higher 28-day in-hospital mortality (demographic-adjusted HR, 1.94 [95% CI, 1.09-3.44]).

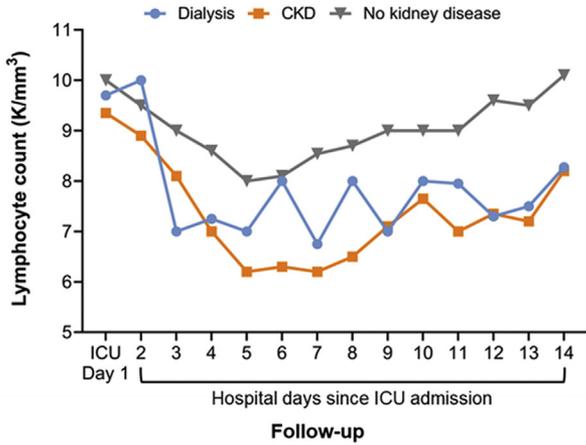
Discussion

In this study of more than 4,200 critically ill adults admitted to 68 U.S. ICUs with COVID-19, we found that having pre-existing kidney disease was associated with higher in-hospital mortality rates, with the strength of this association varying by the degree of baseline kidney dysfunction. Compared to no pre-existing CKD, the presence of pre-existing maintenance dialysis-dependent kidney failure was associated with the highest hazard of in-hospital death, while pre-existing non-dialysis-dependent CKD had an intermediate association. Our findings highlight the importance of identifying effective COVID-19 therapies that can be safely administered to patients with an underlying kidney dysfunction. Moreover, they underscore the urgency of proactive pre-hospital advance care planning conversations with this vulnerable population.

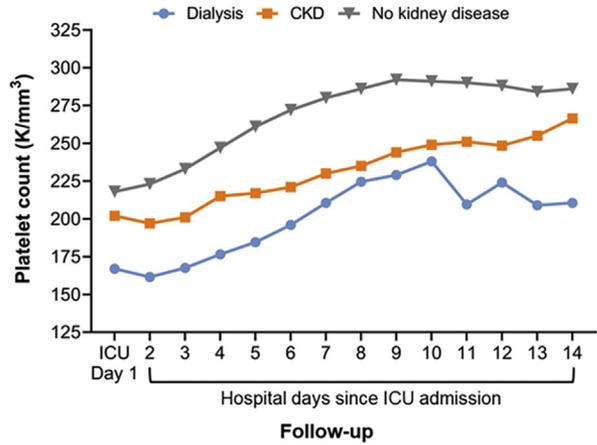
Our findings from a large geographically diverse sample of critically ill COVID-19 patients expand on the existing evidence base demonstrating higher in-hospital mortality among patients with underlying kidney disease and newly report detailed clinical trajectories and outcomes among non-dialysis-dependent CKD patients. The observed association between pre-existing kidney disease (dialysis and non-dialysis-dependent) and in-hospital mortality persisted in models adjusted for medical conditions known to associate with poorer COVID-19 outcomes, suggesting that underlying kidney disease confers risk for individuals with severe COVID-19 beyond that related to the comorbid disease burden characteristic of the disease state. Such findings may relate, in part, to uremia-induced innate immune system changes that hinder neutrophil, monocyte, and B- and T-cell function, thereby impairing bactericidal capacity and antimicrobial ability.¹¹⁻¹³

We also found that maintenance dialysis patients receiving ICU-level care for COVID-19 had an in-hospital death rate of 50%, which is lower than rates reported in regional studies.³⁶⁻³⁸ Strikingly, the unadjusted death rate among non-dialysis-dependent CKD patients (51%) was equivalent to that of dialysis patients (50%) and notably higher than that of patients without underlying CKD (35%). These findings not only highlight the importance of discussing COVID-19 risks with dialysis and non-dialysis-dependent CKD patients, but also highlight the importance of engaging in advance care planning

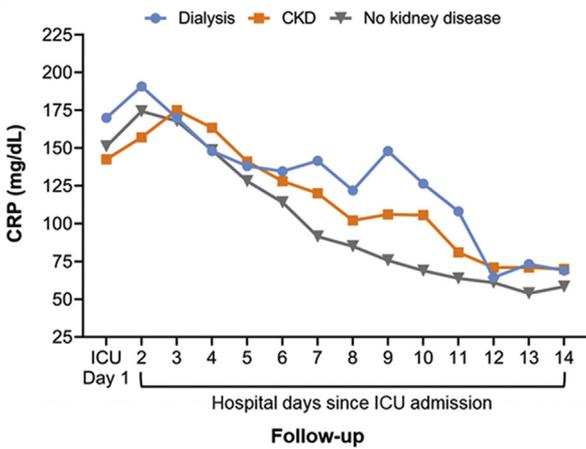
A) Lymphocytes



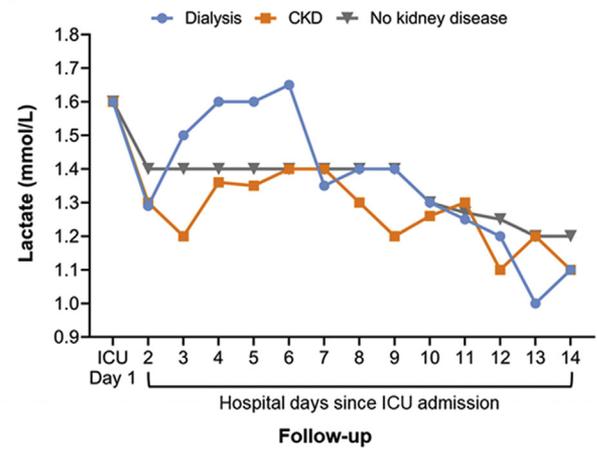
B) Platelets



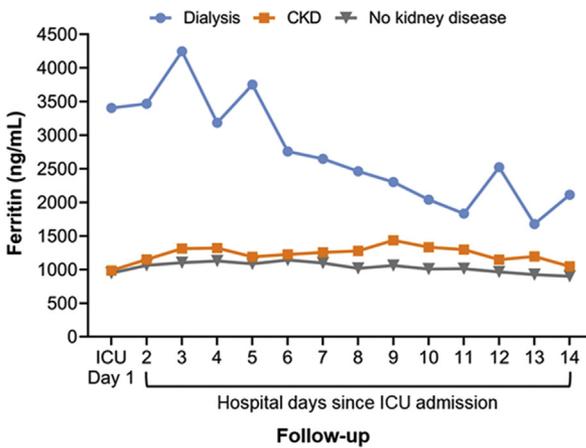
C) CRP



D) Lactate



E) Ferritin



F) Troponin T

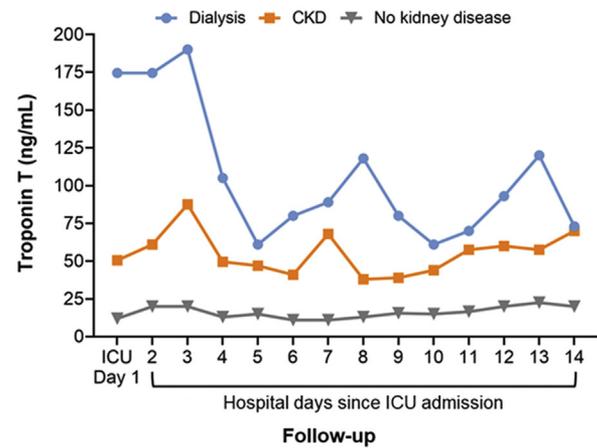
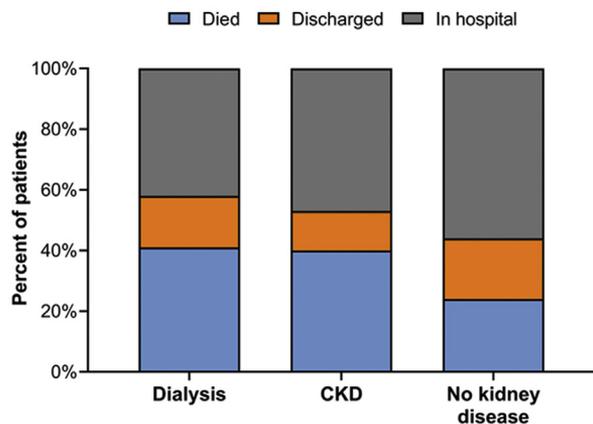


Figure 1. Trajectories of key laboratory values in the first 14 days after intensive care unit (ICU) admission. Median values are presented in the figure. Dialysis represents patients with pre-existing kidney failure receiving maintenance dialysis. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing CKD. [Figure S1](#) displays analogous figures for the laboratory values of creatinine, interleukin 6, fibrinogen, D-dimer, direct bilirubin, and troponin I. Abbreviations: CKD, chronic kidney disease; CRP, C-reactive protein.

A) 14 days after ICU admission



B) 28 days after ICU admission

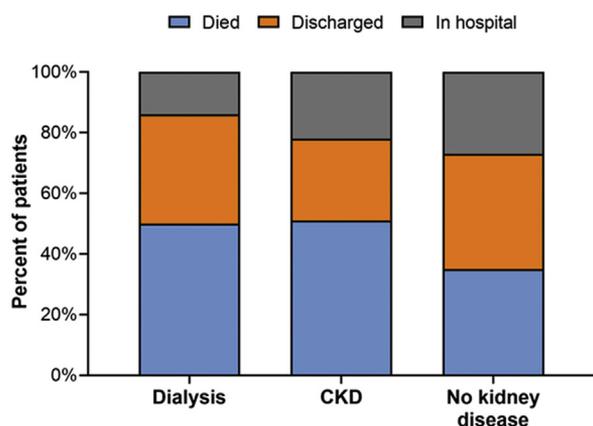


Figure 2. Patient disposition at 14 and 28 days after intensive care unit (ICU) admission. Dialysis represents patients with pre-existing kidney failure receiving maintenance dialysis. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing CKD. Abbreviation: CKD, chronic kidney disease.

conversations in the ambulatory setting, prior to patients falling ill with COVID-19. These discussions are particularly germane for individuals with kidney disease because remdesivir, one of the few evidence-based COVID-19 therapeutic options currently available, is generally not recommended for adults with an eGFR < 30 mL/min/1.73 m².³⁹ However, the purported risks of remdesivir in the setting of kidney dysfunction stem from concerns related to accumulation of its carrier, sulfobutylether-β-cyclodextrin, may be overstated.³⁹ Moreover, individuals with kidney dysfunction are being excluded from clinical trials of other potential therapeutic agents (eg, favipiravir [Clinicaltrials.gov identifier NCT04358549⁴⁰]). Such exclusions may represent yet another example of “renalism” and deserve healthy skepticism by the nephrology community.⁴¹ Lack of safe and effective therapeutic options for patients with COVID-19 and reduced kidney function is a critical gap in our clinical repertoire.

Beyond their elevated in-hospital mortality risks, individuals with pre-existing CKD (dialysis and non-dialysis-dependent) had different symptoms prior to ICU admission than patients without pre-existing CKD. For example, altered mental status afflicted 25% of maintenance dialysis patients compared to just 12% of patients without pre-existing CKD. Dialysis patients have unique neurologic vulnerability related to vascular disease, and dialysis treatment-induced ischemia and osmolar shifts that may leave them susceptible to both the direct (ie, neuroinvasion) and indirect (ie, oxidative stress, hypoxia, and ischemia) neurologic effects of severe COVID-19.^{42,43} In addition, a lower percentage of patients with pre-existing CKD (dialysis and non-dialysis-dependent) reported respiratory symptoms (shortness of breath and cough) and fever compared to patients without pre-existing CKD. These findings are consistent with existing reports^{23,37} and highlight the necessity of vigilance for nontraditional COVID-19 symptoms such as altered mental status and gastrointestinal symptoms.

Finally, given the rapidly changing COVID-19 therapeutic landscape, the timing of our study cohort deserves

Table 4. Association Between Pre-existing CKD and 14- and 28-Day In-Hospital Mortality Among Critically Ill COVID-19 Patients

Patient Group	No. of Deaths	Unadjusted HR (95% CI)	Model 1 HR (95% CI) ^a	Model 2 HR (95% CI) ^b
14-Day In-Hospital Mortality				
No pre-existing CKD	876	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-dialysis-dependent CKD	207	1.80 (1.55-2.09)	1.44 (1.23-1.68)	1.32 (1.13-1.55)
Maintenance dialysis	59	1.89 (1.46-2.45)	1.75 (1.35-2.28)	1.56 (1.19-2.04)
28-Day In-Hospital Mortality				
No pre-existing CKD	1,261	1.00 (reference)	1.00 (reference)	1.00 (reference)
Non-dialysis-dependent CKD	265	1.67 (1.47-1.91)	1.35 (1.18-1.55)	1.25 (1.08-1.44)
Maintenance dialysis	72	1.67 (1.31-2.12)	1.58 (1.24-2.02)	1.41 (1.09-1.81)

Note: Fine and Gray proportional subdistribution hazards models were used to estimate the association between the presence of pre-existing kidney disease (kidney failure receiving maintenance dialysis and non-dialysis-dependent CKD, separately) versus no pre-existing CKD and 14- and 28-day in-hospital mortality. Hospital discharge was treated as a competing event.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HR, hazard ratio, No., number.

^aModel 1 was adjusted for age, sex, race, and Hispanic ethnicity.

^bModel 2 was adjusted for model 1 covariates plus diabetes, hypertension, coronary artery disease, heart failure, and atrial fibrillation or flutter.

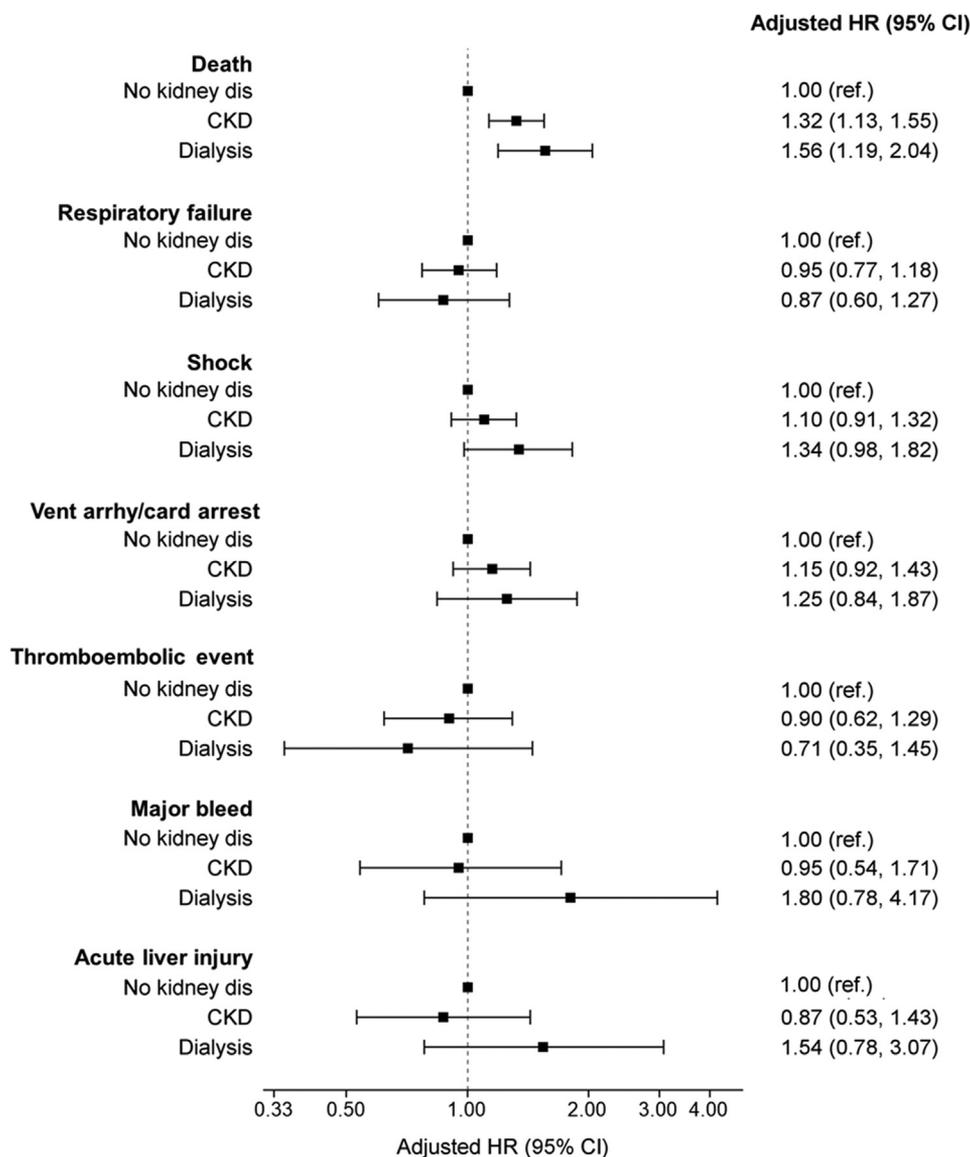


Figure 3. Association between pre-existing CKD and 14-day in-hospital outcomes among critically ill patients with COVID-19. Dialysis represents patients with pre-existing kidney failure receiving maintenance dialysis. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing CKD. Fine and Gray proportional subdistribution hazards models were used to estimate the association between the presence of pre-existing CKD (kidney failure receiving maintenance dialysis and non-dialysis-dependent CKD, separately) versus no pre-existing CKD and 14-day in-hospital outcomes. In mortality analyses, hospital discharge was treated as a competing event. In analyses of other outcomes, both in-hospital death and hospital discharge were treated as competing events. Analyses assessing mortality, respiratory failure, shock, and ventricular arrhythmia or cardiac arrest were adjusted for age, sex, race, Hispanic ethnicity, diabetes, hypertension, coronary artery disease, heart failure, and atrial fibrillation or flutter. Analyses evaluating thrombotic events, major bleeding events, and acute liver injury were only adjusted for age, sex, race, and Hispanic ethnicity due to the low number of event counts. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; HR, hazard ratio; ref., referent; vent arrhyth/card arrest, ventricular arrhythmia or cardiac arrest.

consideration. We studied critically ill individuals who were admitted to ICUs between March 4 and May 10, 2020. This period was relatively early in the US COVID-19 pandemic when cases and mortality were surging in the Northeast, and there were few proven effective treatments (although remdesivir was showing potential). In the intervening months, there have been important therapeutic advances. Several randomized controlled trials have

demonstrated that systemic steroid therapy reduces mortality among critically ill patients with COVID-19.⁴⁴ Smaller studies have suggested benefit from prone positioning.⁴⁵⁻⁴⁷ In addition, on August 23, 2020, the US Food and Drug Administration issued an emergency use authorization for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.⁴⁸ We did not design our observational study to evaluate the

effect of specific therapeutics on outcomes, but instead shine light on the critical importance of testing and identifying therapies that are safe and effective for individuals with a pre-existing kidney dysfunction. Beyond the imperative to include patients with kidney disease in trials of COVID-19 therapeutics, future studies should examine the efficacy and safety of evidence-based therapies in individuals with underlying CKD. Moreover, investigations of temporal and geographic trends of evidence-based therapies to determine whether proven therapies are achieving adequate clinical uptake among individuals with underlying kidney disease are warranted.

Our study has several strengths. First, we used data from a cohort of more than 4,200 critically ill individuals with COVID-19 who were admitted to 68 geographically diverse US ICUs, increasing the generalizability of our findings and expanding the evidence base about critically ill patients with COVID-19 and pre-existing CKD. Second, we performed detailed chart reviews using standardized data extraction tools to collect granular information on patients' clinical courses. This obviated the need for reliance on administrative billing codes that may lead to misclassification and supported the study of detailed comparisons across study groups. Third, data were collected from critically ill patients consecutively admitted to each ICU, minimizing potential selection bias. Fourth, whereas some prior studies of maintenance dialysis patients hospitalized with COVID-19 had limited follow-up time, we followed up patients until the occurrence of hospital discharge, death, or 28 days.

We also acknowledge several study limitations. First, as with all observational studies, residual confounding may exist. However, to examine the association between underlying kidney disease and outcomes independent of coexistent medical conditions, we accounted for key demographic factors and comorbid conditions known to have strong associations with outcomes in individuals with COVID-19 in our multivariable models. Second, we defined pre-existing kidney disease based on the presence of prior eGFR assessments or documentation of CKD in the admitting hospital's medical record. It is possible that some exposure misclassification may have occurred. Third, data for organ injury and organ support were captured during the first 14 days following ICU admission only. Events after the 14-day period may have been missed. However, it is reassuring that most of the observed events occurred early in ICU courses, suggesting that most events were likely captured. Fourth, data on inflammatory markers were not available for many patients (Table S12) and may not have been missing at random (ie, laboratory values were likely drawn more often in patients with more severe COVID-19). As such, it is possible that the observed trends in such markers may not generalize to individuals with less severe COVID-19. Related, it is possible that individuals with pre-existing CKD (dialysis and non-dialysis-dependent) may have been preferentially declined ICU admission or died before ICU admission, raising the possibility of potential selection

bias in our cohort. However, such selection bias would likely bias our findings toward the null. Fifth, we did not have information for 14- and 28-day vital status for patients who were discharged from the hospital before these time points. Finally, limited numbers of some secondary outcomes (eg, major bleeding events and acute liver injury) in the pre-existing CKD groups (dialysis and non-dialysis-dependent) may have limited our ability to detect significant associations. Therefore, these findings should be considered hypothesis generating and fodder for future study.

In conclusion, in this multicenter, nationally representative cohort of US adults with COVID-19 critical illness, we found that both non-dialysis-dependent CKD patients and kidney failure patients receiving maintenance dialysis had a 28-day in-hospital mortality rate of ~50% and patients with underlying kidney disease had higher in-hospital mortality than patients without pre-existing CKD, with maintenance dialysis patients having the highest risk in adjusted analyses. As evidenced by differences in symptoms and clinical trajectories, patients with pre-existing kidney disease may have unique vulnerability to COVID-19-related complications that warrant additional study and special consideration in the pursuit and development of targeted therapies.

Supplementary Material

Supplementary File (PDF)

Figure S1: Trajectories of other laboratory values in the first 14 days after ICU admission.

Figure S2: Contributing cause(s) of death.

Item S1: List of participating STOP-COVID sites.

Item S2: List of STOP-COVID Investigators.

Table S1: Outcome definitions.

Table S2: Patient characteristics on ICU day 1, dialysis patients vs non-dialysis-dependent CKD patients.

Table S3: Patient characteristics on ICU day 1, dialysis patients vs patients without pre-existing CKD.

Table S4: Patient characteristics on ICU day 1, non-dialysis-dependent CKD patients vs patients without pre-existing CKD.

Table S5: Standardized differences comparing therapies administered in the first 14 days after ICU admission.

Table S6: Percentage of 14- and 28-day in-hospital deaths that occurred earlier and later in the study period.

Table S7: Association between pre-existing kidney disease and 14-day in-hospital outcomes.

Table S8: Sensitivity analyses excluding patients on therapeutic anticoagulation on ICU day 1.

Table S9: Sensitivity analyses excluding patients with history of liver disease.

Table S10: Association between baseline serum creatinine and 14- and 28-day in-hospital mortality.

Table S11: Association between vascular access type and 14- and 28-day in-hospital mortality.

Table S12: Association between dialysis vintage and 14- and 28-day in-hospital mortality.

Table S13: ICU day 1 variables with missing data.

Article Information

STOP-COVID Investigators: A full list of the STOP-COVID Investigators is provided in [Item S2](#).

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Outcomes of Patients with Kidney Disease and Severe COVID-19

Methods & Cohort	Results	
<p>Retrospective cohort study</p>  <p>4,264 critically ill adults with COVID-19 from 68 ICUs in the US</p>  <p>Admitted to the ICU between Mar 4 - May 10, 2020</p>	<p>Pre-existing kidney disease</p>  <p>Patient group</p> <p> Dialysis-dependent (N = 143)</p> <p> Chronic kidney disease (N = 521)</p> <p> No kidney disease (N = 3,600)</p>	<p>28-day in-hospital death</p>  <p>Absolute death rate</p> <p>Adjusted HR (95% CI)</p> <p>50% 1.41 (1.09, 1.81)</p> <p>51% 1.25 (1.08, 1.44)</p> <p>35% Reference</p>

CONCLUSION: Among critically ill adults with COVID-19, having pre-existing kidney disease was associated with higher risk of 28-day in-hospital death.

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