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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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ABSTRACT

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

Study Design: Retrospective cohort study

Settings & Participants: 4,264 critically ill COVID-19 patients (143 dialysis patients, 521 chronic kidney disease [CKD] patients, and 3,600 patients without CKD) admitted to ICUs at 68 hospitals in the United States.

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

Outcome(s): In-hospital mortality (primary); respiratory failure, shock, ventricular arrhythmia/cardiac arrest, thromboembolic event, major bleed, 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 [quartile 1-quartile 3] days: 4 [2-9] for dialysis patients; 7 [3-10] for CKD patients; 7 [4-10] for patients without pre-existing kidney disease). More dialysis patients (25%) reported altered mental status than those with CKD (20%, standardized difference = 0.12) and no kidney disease (12%, standardized difference = 0.36). Half of dialysis and CKD patients died within 28-days of ICU admission versus 35% of patients without pre-existing kidney disease. Compared to patients without pre-existing kidney disease, dialysis patients had a higher risk of 28-day in-hospital death (adjusted HR 1.41; 95% CI 1.09, 1.81), while patients with 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 for this vulnerable population.

**Index words:** SARS-CoV-2, COVID-19, critical illness, chronic kidney disease, end stage kidney disease, dialysis
PLAIN LANGUAGE SUMMARY

Individuals with underlying kidney disease may be particularly vulnerable to severe COVID-19 illness, marked by multi-system 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 U.S., we found that both chronic kidney disease and dialysis patients had a ~50% 28-day in-hospital mortality rate. Patients with underlying kidney disease had higher in-hospital mortality than patients without kidney disease, with patients on 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.
INTRODUCTION

Since its emergence in Wuhan, China in late 2019, the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has snowballed into a global pandemic, infecting over 28 million people across the globe and killing more than 900,000 as of mid-September 2020. Emerging data suggest that individuals with underlying kidney dysfunction have worse COVID-19-related outcomes than those without kidney dysfunction. Similar outcome differences across patients with and without kidney dysfunction have been observed in other illness states (e.g., general critical illness, influenza), and may relate, in part, to the innate immunity impairment, vascular dysfunction, and heightened inflammatory state that are characteristic of advanced kidney disease (CKD).

As such, individuals with underlying kidney dysfunction 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. Data from the United States (U.S.) indicate that patients with critical COVID-19 illness complicated by acute kidney injury (AKI) have worse outcomes than those without AKI. Single-center and regional studies suggest similarly poor outcomes among individuals with critical COVID-19 illness and pre-existing kidney dysfunction, especially dialysis-dependent kidney failure, but sample sizes were limited, and most lacked comparator populations. Given the rapidly changing landscape of COVID-19 therapeutics and potential for impaired kidney function to limit therapeutic options (e.g., remdesivir), granular, broadly representative data characterizing clinical courses of critically ill patients with COVID-19 and pre-existing kidney disease are needed to inform management of this vulnerable population.
To address this knowledge gap, we used data from Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), a cohort study of >4,000 patients with COVID-19 admitted to ICUs at 68 hospitals across the U.S., and examined the clinical courses of critically ill COVID-19 patients with and without pre-existing kidney disease. We also investigated the association between degree of underlying kidney disease and occurrence of in-hospital mortality and other outcomes (e.g., respiratory failure, shock, thromboembolic events).

**METHODS**

**Patient Population and Study Design**

We used data from STOP-COVID, a multicenter cohort study that enrolled consecutive adults (≥18 years old) with laboratory-confirmed COVID-19 admitted to ICUs at 68 geographically diverse U.S. hospitals (Supplemental Material). Cohort compilation and initial results have been previously reported.\(^{26}\) The STOP-COVID parent study was approved by the institutional review boards (IRBs) at each participating site. This ancillary study was approved by the University of North Carolina at Chapel Hill IRB (#20-1395). A waiver of informed consent was granted due to the anonymity of the STOP-COVID limited dataset used for this project.

In this study focused on pre-existing kidney disease, we included 4,264 critically ill COVID-19 patients with and without pre-existing kidney disease admitted to 68 ICUs 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 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, comorbidities, 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 dialysis-dependent kidney failure, we also collected data on dialysis modality, length of time receiving maintenance dialysis, and vascular access type (for hemodialysis patients), all preceding hospital admission.

**Exposures**

The exposures of interest were the presence of pre-existing CKD and dialysis-dependent kidney failure. We defined pre-existing 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] Study\(^27\) or CKD Epidemiology Collaboration [CKD-EPI] equations\(^28\)) 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 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 dialysis-dependent kidney failure as medical chart-documented maintenance dialysis therapy prior to hospital admission. We categorized patients without evidence of CKD or dialysis-dependent kidney failure as having no pre-existing kidney disease.

**Outcomes**
The primary outcomes were 14- and 28-day in-hospital mortality. The secondary outcomes included 14-day in-hospital respiratory failure, shock, ventricular arrhythmia or cardiac arrest, thromboembolic event (including ischemic stroke, pulmonary embolism, or deep vein thrombosis), major bleed, and acute liver injury (Supplemental Table S1).

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). We described patient characteristics on ICU day 1, therapies administered, and laboratory parameters across exposure groups as count (%) for categorical variables and as median [quartile 1, quartile 3] 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 kidney disease (CKD and dialysis-dependent ESKD, separately) vs. no pre-existing kidney disease 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 prior to hospital admission and dialysis vintage (separately) and mortality in hemodialysis patients, and the degree of baseline creatinine (pre-hospital serum creatinine <1.2, 1.2-1.9, and ≥2.0 mg/dL) and mortality in CKD patients.

We used similar methods to examine the association between the presence (vs. absence) of pre-existing kidney disease 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, while 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 on therapeutic-level anticoagulation on ICU day 1 from models examining major bleed and thromboembolic events, and excluding patients with histories 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 dialysis-dependent kidney failure, 521 (12%) with pre-existing non-dialysis-dependent CKD, and 3,600 (85%) without pre-existing kidney disease. Table 1 and Supplemental Tables S2-S4 display the demographic and clinical characteristics on ICU day 1 across study groups. The majority of patients in the study (58%) were cared for in ICUs located in the northeastern U.S. CKD patients were older than dialysis patients (median [quartile 1–quartile 3] age: 69 [60-76] and 65 [56-71] years, respectively, ASMD = 0.31) and patients without pre-existing kidney disease (median age 61 [51-70] years, ASMD = 0.55). Comorbid conditions including diabetes and cardiovascular conditions were more common in patients with
pre-existing kidney disease (both dialysis-dependent and CKD) compared to those without.

Of the 143 individuals with pre-existing dialysis-dependent kidney failure, 128 (90%) received in-center hemodialysis, 9 (6%) received peritoneal dialysis, 2 (1%) received home hemodialysis, and 4 (3%) had an undocumented modality prior to hospital admission. Of the 128 hemodialysis patients with 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 [2-9] days among dialysis patients, 7 [3-10] days among CKD patients, and 7 [4-10] days among patients without pre-existing kidney disease. In general, dialysis patients reported COVID-19-related symptoms prior to ICU admission at a lower frequency than patients without kidney disease, with one exception: the percentage of dialysis patients reporting altered mental status was more than twice that of patients without kidney disease (25% vs. 12%, ASMD = 0.36) and slightly more than patients with CKD (25% vs. 20%, ASMD = 0.12). In addition, respiratory symptoms were less frequent in dialysis patients compared to the other groups.

Table 2 and Supplemental Tables S2-S4 display COVID-19 severity and laboratory findings on ICU day 1 across study groups. A modestly higher percentage of patients without kidney disease (63%) required invasive mechanical ventilation on ICU day 1 compared to dialysis patients (56%, ASMD = 0.15). Median white cell counts, platelet counts, and fibrinogen concentrations on ICU day 1 were lower in dialysis patients compared to patients without kidney disease, whereas median C-reactive protein, interleukin-6, ferritin, and troponin levels were higher in dialysis patients (all ASMDs >0.10). Similar laboratory patterns were observed for platelet count, fibrinogen, and troponin levels when comparing CKD patients to patients without kidney disease, but the differences were of lower magnitudes.
Targeted Therapies and Clinical Trajectories

Table 3 displays COVID-19-targeted therapies administered during the 14 days after ICU admission in each group (Supplemental Table S5: corresponding ASMDs). Compared to dialysis patients, a higher percentage of patients without pre-existing kidney disease were mechanically ventilated (74% vs. 80%, ASMD = 0.15). Proned positioning was used in a higher percentage of patients without kidney disease (42%) compared to CKD (27%, ASMD = 0.30) and dialysis (24%, ASMD = 0.37) patients. Remdesivir was more commonly administered to patients without kidney disease (7%) compared to CKD patients (2%, ASMD = 0.22). No dialysis patients received remdesivir. Patients without kidney disease received tocilizumab (19%) more often than those with CKD (14%, ASMD = 0.12) and dialysis-dependent kidney failure (9%, ASMD = 0.28).

Figure 1 and Supplemental Figure S1 display laboratory parameter trajectories during the first 14 days after ICU admission across groups. In general, dialysis and CKD patients had lower platelet counts and higher levels of C-reactive protein compared to patients without kidney disease. 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 kidney disease.

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 (Supplemental Figure S2). Compared to no pre-existing kidney disease, pre-existing CKD and dialysis-dependent kidney failure 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 (i.e. models adjusted for demographic and comorbid conditions), the associations were slightly attenuated but remained statistically significant (fully adjusted HR (95% CI) for 28-day in-hospital mortality): 1.25 (1.08, 1.44) for CKD and 1.41 (1.09, 1.81) for dialysis-dependent kidney failure. Models evaluating 14-day in-hospital mortality produced similar results. Of the patients who died during the 28-days following ICU admission, the median [quartile 1–quartile 3] time from ICU admission to death was 8 [5-11], 8 [5-13], and 10 [6-16] days for the dialysis, CKD, and no kidney disease groups, respectively. Mortality rates across exposure groups were stable during the study period (Supplemental Table S6).

Figure 3 and Supplemental Table S7 display secondary outcomes across patient groups. Dialysis patients trended toward having higher risks of shock, ventricular arrhythmia or cardiac arrest, major bleeding events, and acute liver injury during the 14 days after ICU admission. 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 patients with histories of liver disease from acute liver injury models produced similar results (Supplemental Tables S8-S9).

Pre-existing Kidney Disease Subgroups

Supplemental Tables S10-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 creatinine levels, a higher baseline creatinine trended toward associations with higher in-hospital mortality, but results did not reach statistical significance. Among the 128 in-center hemodialysis patients, dialysis via a catheter (vs. arteriovenous access) was associated with higher 28-day in-hospital mortality, demographic-adjusted HR (95% CI): 1.94 (1.09, 3.44).
DISCUSSION

In this study of over 4,200 critically ill adult patients 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 degree of baseline kidney dysfunction. Compared to no pre-existing kidney disease, the presence of pre-existing kidney failure (dialysis-dependent) was associated with the highest hazard of in-hospital death, while pre-existing CKD (non-dialysis-dependent) had an intermediate association. Our findings highlight the importance of identifying effective COVID-19 therapies that can be safely administered to patients with underlying kidney dysfunction. Moreover, they underscore the urgency of proactive, pre-hospital advanced 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 CKD patients. The observed association between pre-existing kidney disease 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 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.\textsuperscript{36-38} Strikingly, the unadjusted death rate among CKD patients (51%) was equivalent to that of dialysis patients (50%) yet notably higher than that of patients without underlying kidney disease (35%). These findings not only highlight the importance of discussing COVID-19 risks with both dialysis and CKD patients, but also engaging in advanced care planning conversations in the ambulatory setting, prior to patients falling ill with COVID-19. These discussions are particularly germane for individuals with kidney disease since 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/1.73m\(^2\).\textsuperscript{39} However, the purported risks of remdesivir in the setting of kidney dysfunction that stem from concerns related to accumulation of its carrier, sulfobutylether-\(\beta\)-cyclodextrin, may be overstated.\textsuperscript{39} Moreover, individuals with kidney dysfunction are being excluded from clinical trials of other potential therapeutic agents (e.g. favipiravir, NCT04358549\textsuperscript{40}). Such exclusions may represent yet another example of “renalism” and deserve healthy skepticism by the nephrology community.\textsuperscript{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 kidney disease had different symptom prior to ICU admission than patients without kidney disease. For example, altered mental status afflicted 25% of dialysis patients compared to just 12% of patients without pre-existing kidney disease. 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 (i.e. neuro-invasion) and indirect (i.e. oxidative stress, hypoxia, and ischemia) neurological effects of severe COVID-19.\textsuperscript{42, 43} In addition, a lower
percentage of patients with pre-existing kidney disease (dialysis-dependent and CKD) reported respiratory symptoms (shortness of breath and cough) and fever compared to patients without kidney disease. These findings are consistent with existing reports\textsuperscript{23, 37} and highlight the necessity of vigilance for non-traditional 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 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 U.S. 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 steroids reduce mortality among critically ill patients with COVID-19.\textsuperscript{44} Smaller studies have suggested benefit from prone positioning.\textsuperscript{45-47} In addition, on August 23, 2020, the Food and Drug Administration issued an emergency use authorization for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19.\textsuperscript{48} We did not design our observational study to evaluate the effect of specific therapeutics on outcomes, but instead to shine light on the critical importance of testing and identifying therapies that are safe and effective for individuals with 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 kidney disease. Moreover, investigations of temporal and geographic trends of evidence-based therapies to determine if 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 over 4,200 critically ill individuals with COVID-19 who were admitted to 67 geographically diverse U.S. ICUs, increasing the generalizability of our findings and substantially expanding the evidence base about critically ill COVID-19 patients with pre-existing kidney disease. Second, we performed detailed chart reviews using standardized data extraction tools to collect daily, 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 dialysis patients hospitalized with COVID-19 had limited follow-up time, we followed 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 measurements or documentation of CKD in the admitting hospital’s medical record. It is possible that some exposure misclassification may have occurred. Third, data on organ injury and organ support were captured during the first 14 days following ICU admission only. Events after the 14-day time period may have been missed. However, it is reassuring that most of the observed events occurred early in ICU courses, suggesting that the majority of events were likely captured. Fourth, data on inflammatory markers were not available for many patients (Supplemental Table S12) and may not have been
missing at random (i.e., 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 kidney disease may have been preferentially declined ICU admission or died prior to 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 on 14- and 28-day vital status for patients discharged from the hospital prior to these time points. Finally, limited numbers of some secondary outcomes (e.g., major bleeding events, acute liver injury) in the pre-existing kidney disease groups 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 U.S. adults with COVID-19 critical illness, we found that both CKD and dialysis patients had a ~50% 28-day in-hospital mortality rate and that patients with underlying kidney disease had higher in-hospital mortality than patients without kidney disease, 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**

List of STOP-COVID investigators

List of participating STOP-COVID sites
Supplemental Figure S1. Trajectories of other laboratory values in the first 14 days after ICU admission

Supplemental Figure S2. Contributing cause(s) of death

Supplemental Table S1. Outcome definitions

Supplemental Table S2. Characteristics of critically ill COVID-19 patients with pre-existing dialysis-dependent kidney failure and CKD on ICU day 1

Supplemental Table S3. Characteristics of critically ill COVID-19 patients with pre-existing dialysis-dependent kidney failure and no pre-existing kidney disease on ICU day 1

Supplemental Table S4. Characteristics of critically ill COVID-19 patients with pre-existing CKD and no pre-existing kidney disease on ICU day 1

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

Supplemental Table S7. Association between pre-existing kidney disease and 14-day in-hospital outcomes among critically ill COVID-19 patients
Supplemental Table S8. Sensitivity analyses evaluating the association between pre-existing kidney disease and 14-day in-hospital major bleeding and thromboembolic events excluding patients on therapeutic anticoagulation on ICU day 1

Supplemental Table S9. Sensitivity analyses evaluating the association between pre-existing kidney disease and 14-day in-hospital acute liver injury excluding patients with histories of liver disease

Supplemental Table S10. Association between baseline serum creatinine and 14- and 28-day in-hospital mortality among critically ill CKD patients with COVID-19

Supplemental Table S11. Association between vascular access type and 14- and 28-day in-hospital mortality among critically ill hemodialysis patients with COVID-19

Supplemental Table S12. Association between dialysis vintage and 14- and 28-day in-hospital mortality among critically ill hemodialysis patients with COVID-19

Supplemental Table S13. ICU day 1 variables with missing data

Article Information

AUTHORS’ CONTRIBUTIONS: Research idea and study design: JEF, MMA; data acquisition: all authors; data analysis/interpretation: all authors; statistical analysis: MMA; supervision or mentorship: JEF, DEL. Each author contributed important intellectual content.
during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

SUPPORT: JEF and MMA are supported by R01 HL152034 from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). JEF is supported by K23 DK109401 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the NIH. FPW is supported by R01DK113191 and P30DK097310 from the NIDDK of the NIH. SA is supported by K23 DK101826 from the NIDDK of the NIH. MC is supported by the Westchester Community Foundation – Renal Clinic Fund. DEL is supported by R01DK125786 from the NIDDK of the NIH and R01HL144566 from the NHLBI of the NIH. The funders played no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

FINANCIAL DISCLOSURES: In the last 3 years, JEF received speaking honoraria from American Renal Associates, American Society of Nephrology, Dialysis Clinic, Inc., National Kidney Foundation, and multiple universities as well as investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America. JEF is on the medical advisory board of NxStage Medical, Inc. and has received consulting fees from Fresenius Medical Care, North America and AstraZeneca. In the last 3 years, MMA received investigator-initiated research funding from the Renal Research Institute, a subsidiary of Fresenius Medical Care, North America and honoraria from the International Society of Nephrology. In the last 3 years, EHC received investigator-initiated funding from the Renal
Research Institute, a subsidiary of Fresenius Medical Care, North America. SG is a scientific coordinator for Glaxo Smith Kline’s ASCEND trial. In the last 3 years, SA received the Normon S. Coplon Applied Pragmatic Research Award sponsored by Satellite Health Care and has consulted for DURECT. All other authors have nothing to disclose.

ACKNOWLEDGEMENTS: The authors thank the study site research teams who invested countless hours in electronic health record review and data entry.

Peer Review: Received July 24, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor and an Associate Editor, who served as Acting Editor-in-Chief. Accepted in revised form September 15, 2020. The involvement of an Acting Editor-in-Chief was to comply with AJKD’s procedures for potential conflicts of interest for editors, described in the Information for Authors & Journal Policies.

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Table 1. Characteristics of critically ill COVID-19 patients on ICU day 1

| Characteristica | Dialysis-dependent kidney failure n = 143 | Chronic kidney disease n = 521 | No pre-existing kidney disease n = 3600 |
|-----------------|------------------------------------------|-------------------------------|--------------------------------------|
| **Demographics** |                                         |                               |                                      |
| Age (years)     | 65 [56-71]                               | 69 [60-76]                    | 61 [51-70]                           |
| Male            | 77 (54%)                                 | 323 (62%)                     | 2314 (64%)                          |
| Racea           |                                         |                               |                                      |
| White           | 48 (34%)                                 | 184 (35%)                     | 1403 (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%)                          |
| **Ethnicitya**  |                                         |                               |                                      |
| Hispanic        | 29 (20%)                                 | 66 (13%)                      | 919 (26%)                           |
| Non-Hispanic    | 107 (75%)                                | 411 (79%)                     | 2218 (62%)                          |
| Unknown/not reported | 7 (5%)                              | 44 (8%)                       | 463 (13%)                          |
| BMI (kg/m²)     | 28.3 [23.8-34.7]                         | 30.3 [26.3-36.3]              | 30.4 [26.5-35.6]                    |
| **U.S. geographic region** |                                 |                               |                                      |
| Northeast       | 78 (55%)                                 | 241 (46%)                     | 2175 (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%)                     | 1337 (37%)                          |
| Hypertension    | 125 (87%)                                | 451 (87%)                     | 2036 (57%)                          |
| Coronary artery disease | 55 (38%)                           | 146 (28%)                     | 374 (10%)                           |
| Heart failure   | 44 (31%)                                 | 136 (26%)                     | 233 (6%)                            |
| Atrial fibrillation or flutter | 31 (22%)                           | 79 (15%)                      | 211 (6%)                            |
| Asthma or COPD  | 21 (15%)                                 | 118 (23%)                     | 617 (17%)                           |
| Chronic liver disease | 7 (5%)                              | 33 (6%)                       | 103 (3%)                            |
| **Home medications** |                                         |                               |                                      |
| ACE inhibitor or ARB | 35 (24%)                             | 243 (47%)                     | 1127 (31%)                          |
| Beta blocker    | 98 (69%)                                 | 264 (51%)                     | 768 (21%)                           |
| Other antihypertensive | 69 (48%)                           | 296 (57%)                     | 937 (26%)                           |
| Statin          | 80 (56%)                                 | 371 (61%)                     | 1226 (34%)                          |
| Aspirin         | 65 (45%)                                 | 203 (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%)                     | 1981 (55%)                          |
| Hospital ward   | 47 (33%)                                 | 165 (32%)                     | 1114 (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%)                     | 2733 (76%)                          |
| Cough           | 81 (57%)                                 | 322 (62%)                     | 2698 (75%)                          |
| Fever           | 82 (57%)                                 | 294 (56%)                     | 2486 (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%)                           |

Values are n (%) for categorical variables and median [quartile 1 – quartile 3] for continuous variables. Absolute standardized mean differences comparing the patient groups to one another are presented in Supplemental Tables S2-S4. Variables with missing values are presented in Supplemental Table S13.

a Information on ethnicity and race were abstracted from the electronic health record of each patient. In the U.S., people of Hispanic ethnicity are those of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NSAIDs, non-steroidal anti-inflammatory drug; U.S., United States.
Table 2. Illness severity and laboratory findings of critically ill COVID-19 patients on ICU day 1

| Characteristic                     | Dialysis-dependent kidney failure n = 143 | Chronic kidney disease n = 521 | No pre-existing kidney disease n = 3600 |
|------------------------------------|------------------------------------------|-------------------------------|----------------------------------------|
| **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%)                     | 1837 (51%)                             |
| Lowest systolic BP (mmHg)          | 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%)                     | 2284 (63%)                             |
| PEEP (cm H₂O)                      | 10 [8-14]                                | 10 [10-15]                    | 12 [10-15]                             |
| PaO₂:FiO₂ ratio (mmHg)             | 164 [101-267]                            | 125 [79-190]                  | 122 [83-191]                           |
| Non-invasive mechanical ventilation| 3 (2%)                                   | 16 (3%)                       | 86 (2%)                                |
| High-flow nasal cannula or non-rebreather mask | 29 (20%)                             | 121 (23%)                     | 801 (22%)                              |
| AKI requiring dialysis             | --                                       | 27 (5%)                       | 55 (2%)                                |
| **Renal SOFA score**              |                                          |                               |                                        |
| 0 (creatinine < 1.2 mg/dL)         | 0 (0%)                                   | 62 (12%)                      | 2347 (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 RRT)  | 143 (100%)                               | 80 (15%)                      | 83 (2%)                                |
| **Liver SOFA score**              |                                          |                               |                                        |
| 0 (bilirubin < 1.2 mg/dL)          | 132 (92%)                                | 482 (93%)                     | 3253 (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**         |                                          |                               |                                        |
| 0 (platelet count ≥ 150 K/µL³)     | 90 (63%)                                 | 408 (78%)                     | 2989 (83%)                             |
| 1 (platelet count 100-149 K/µL³)   | 37 (26%)                                 | 80 (15%)                      | 467 (13%)                              |
| ≥ 2 (platelet count < 100 K/µL³)   | 16 (11%)                                 | 33 (6%)                       | 144 (4%)                               |
| **Bacteremia or endocarditis**     | 17 (12%)                                 | 75 (14%)                      | 370 (10%)                              |
| **Laboratory findings**            |                                          |                               |                                        |
| White cell count (K/µL³)           | 7.5 [5.7-10.4]                           | 8.2 [5.8-11.6]                | 8.5 [6.1-11.9]                         |
| Lymphocyte count (K/µL³)           | 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]               | 12.6 [11.4-14.2]                       |
| Platelet count (K/µL³)             | 167 [124-212]                            | 202 [155-258]                 | 218 [167-281]                          |
| Creatinine (mg/dL)                 | 7.7 [5.6-10.1]                           | 2.2 [1.5-3.6]                 | 1.0 [0.8-1.4]                          |
| AST (units/L)                      | 46 [30-72]                              | 48 [33-80]                    | 54 [36-85]                             |
| ALT (units/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 [7.2-7.43]                          | 7.34 [7.2-7.40]               | 7.38 [7.3-7.44]                        |
| Fibrinogen (mg/dL)                 | 542 [369-619]                            | 588 [442-732]                 | 614 [491-764]                          |
| D-dimer (ng/mL)                    | 1347 [609-2623]                          | 1385 [670-3018]               | 1270 [652-3459]                        |
| Ferritin (ng/mL)                   | 3406 [1795-6271]                         | 984 [450-1961]                | 947 [489-1919]                         |
| 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]                            |

Values are n (%) for categorical variables and median [quartile 1 – quartile 3] for continuous variables. Absolute standardized mean differences comparing the patient groups to one another are presented in Supplemental Tables S2-S4. Variables with missing values are presented in Supplemental Table S13.

a Renal component of the SOFA score was based on serum creatinine levels. Patients who did not have a serum creatinine drawn on ICU day 1 were classified as having a renal SOFA score of 0, and patients on RRT were classified as having a renal SOFA score of 4. 49

b Liver 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
Coagulation 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

Shock is defined as the requirement of ≥2 vasopressors or inotropes.

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CRP, C-reactive protein; FiO2, fraction of inspired oxygen; IL, interleukin; PaO2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.
| Therapy                          | Dialysis-dependent kidney failure n = 143 | Chronic kidney disease n = 521 | No pre-existing kidney disease n = 3600 |
|---------------------------------|-------------------------------------------|--------------------------------|----------------------------------------|
| **Anti-infective agent**        |                                           |                                |                                        |
| HCQ or CQ                       | 83 (58%)                                  | 352 (68%)                      | 2487 (69%)                             |
| Azithromycin                    | 63 (44%)                                  | 274 (53%)                      | 1959 (54%)                             |
| HCQ or CQ + azithromycin       | 36 (25%)                                  | 127 (24%)                      | 1127 (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              | 52 (36%)                                  | 204 (39%)                      | 1357 (38%)                             |
| Dexamethasone                   | 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%)                      | 2891 (80%)                             |
| Neuromuscular blockade          | 27 (19%)                                  | 163 (31%)                      | 1410 (39%)                             |
| Inhaled epoprostenol            | 1 (1%)                                    | 29 (6%)                        | 185 (5%)                               |
| Inhaled nitric oxide            | 4 (3%)                                    | 19 (4%)                        | 132 (4%)                               |
| Proned positioning              | 35 (24%)                                  | 142 (27%)                      | 1495 (42%)                             |
| ECMO                            | 1 (1%)                                    | 3 (1%)                         | 157 (4%)                               |
| Vasopressor or inotrope         | 106 (74%)                                 | 366 (70%)                      | 2502 (70%)                             |
| Mechanical cardiac support      | 1 (1%)                                    | 1 (0%)                         | 5 (0%)                                 |
| **Other**                       |                                           |                                |                                        |
| Therapeutic anticoagulation     | 64 (45%)                                  | 232 (45%)                      | 1656 (46%)                             |
| Convalescent serum              | 4 (3%)                                    | 10 (2%)                        | 132 (4%)                               |

Values are n (%) of patients. Absolute standardized mean differences comparing the patient groups to one another are presented in Supplemental Table S5.

a The anti-infective medication categories of HCQ or CQ, azithromycin, and HCQ or CQ + azithromycin are not mutually exclusive.

b The anti-inflammatory agent categories of any corticosteroid and dexamethasone are not mutually exclusive.

机械设备 cardiac support included an intra-aortic balloon pump, Impella® heart pump, and left and right ventricular assist devices.

c Therapeutic anticoagulation included continuous drips of heparin, argatroban, or bivalirudin; subcutaneous enoxaparin (1.5 mg/kg once per day), dalteparin (150-200 units/kg once per day or 100 units/kg twice per day; fondaparinux (≥ 5 mg per day); oral anticoagulants (e.g. warfarin, apixaban, rivaroxaban, edoxaban, dabigatran).

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CQ, chloroquine; ECMO, extracorporeal membrane oxygenation; HCQ, hydroxychloroquine; NSAID, non-steroidal anti-inflammatory drug.
### 14-day in-hospital mortality

| Patient group                        | No. of deaths | Unadjusted HR (95% CI) | Model 1 HR (95% CI)<sup>a</sup> | Model 2 HR (95% CI)<sup>b</sup> |
|--------------------------------------|---------------|------------------------|----------------------------------|----------------------------------|
| No pre-existing kidney disease       | 876           | 1.00 (ref.)            | 1.00 (ref.)                      | 1.00 (ref.)                      |
| Chronic kidney disease               | 207           | 1.80 (1.55, 2.09)      | 1.44 (1.23, 1.68)                | 1.32 (1.13, 1.55)                |
| Dialysis-dependent kidney failure    | 59            | 1.89 (1.46, 2.45)      | 1.75 (1.35, 2.28)                | 1.56 (1.19, 2.04)                |

### 28-day in-hospital mortality

| Patient group                        | No. of deaths | Unadjusted HR (95% CI) | Model 1 HR (95% CI)<sup>a</sup> | Model 2 HR (95% CI)<sup>b</sup> |
|--------------------------------------|---------------|------------------------|----------------------------------|----------------------------------|
| No pre-existing kidney disease       | 1261          | 1.00 (ref.)            | 1.00 (ref.)                      | 1.00 (ref.)                      |
| Chronic kidney disease               | 265           | 1.67 (1.47, 1.91)      | 1.35 (1.18, 1.55)                | 1.25 (1.08, 1.44)                |
| Dialysis-dependent kidney failure    | 72            | 1.67 (1.31, 2.12)      | 1.58 (1.24, 2.02)                | 1.41 (1.09, 1.81)                |

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

<sup>a</sup> Model 1 was adjusted for age, sex, race, and Hispanic ethnicity.

<sup>b</sup> Model 2 was adjusted for model 1 covariates plus diabetes, hypertension, coronary artery disease, heart failure, and atrial fibrillation or flutter.

**Abbreviations:** CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; No., number; ref., referent.
FIGURE TITLES, LEGENDS, and ABBREVIATIONS

Figure 1. Trajectories of key laboratory values in the first 14 days after ICU admission

Values presented in the figure are medians. Dialysis represents patients with pre-existing dialysis-dependent kidney failure. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing kidney disease. Supplemental 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; ICU, intensive care unit; IL, interleukin.

Figure 2. Patient disposition at 14 and 28 days after ICU admission

Dialysis represents patients with pre-existing dialysis-dependent kidney failure. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing kidney disease.

Abbreviations: CKD, chronic kidney disease; ICU, intensive care unit.

Figure 3. Association between pre-existing kidney disease and 14-day in-hospital outcomes among critically ill COVID-19 patients

Dialysis represents patients with pre-existing dialysis-dependent kidney failure. CKD represents patients with pre-existing non-dialysis-dependent CKD. No kidney disease represents patients without pre-existing kidney disease. Fine and Gray proportional subdistribution hazards models were used to estimate the association between the presence of pre-existing kidney disease (dialysis-dependent kidney failure and non-dialysis-dependent CKD, separately) vs. no pre-existing kidney disease and 14-day in-hospital outcomes. In mortality analyses, hospital discharge was treated as a competing event. In analyses of other outcomes both 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, Hispanic ethnicity only due to the low number of event counts.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; ref., referent; vent arrhyth/card arrest, ventricular arrhythmia or cardiac arrest.
| Event                         | No kidney dis | CKD             | Dialysis         | Adjusted HR (95% CI) |
|-------------------------------|---------------|-----------------|------------------|---------------------|
| **Death**                     |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 1.32 (1.13, 1.55)| 1.56 (1.19, 2.04)|                     |
| **Respiratory failure**       |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 0.95 (0.77, 1.18)| 0.87 (0.60, 1.27)|                     |
| **Shock**                     |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 1.10 (0.91, 1.32)| 1.34 (0.98, 1.82)|                     |
| **Vent arrhy/card arrest**    |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 1.15 (0.92, 1.43)| 1.25 (0.84, 1.87)|                     |
| **Thromboembolic event**      |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 0.90 (0.62, 1.29)| 0.71 (0.35, 1.45)|                     |
| **Major bleed**               |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 0.95 (0.54, 1.71)| 1.80 (0.78, 4.17)|                     |
| **Acute liver injury**        |               |                 |                  |                     |
|                               | 1.00 (ref.)   | 0.87 (0.53, 1.43)| 1.54 (0.78, 3.07)|                     |