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Original Research

Significance of Chronic Kidney Disease on Morbidity and Mortality in Hospitalized Patients With COVID-19

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Abstract

Background
Patients with comorbid illnesses are at risk for worse outcomes with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19). Our research examined patients with chronic kidney disease (CKD) to establish whether it remains an independent risk factor for mortality and morbidity in patients with COVID-19.

Methods
We conducted a retrospective cohort study using an electronic patient database in 2020. An observational dataset from 149 hospitals comprising a United States-based health system (HCA Healthcare) was analyzed. Hospitalized patients (N=11 086), aged 18 and above, with a COVID-19 polymerase chain reaction positive result between January 1, 2020, and September 1, 2020, were included in the initial data set.

Primary outcomes were in-hospital death or discharge to hospice in patients with COVID-19. Secondary outcomes were individual components of the primary outcome including intensive care unit (ICU) admission, ventilator dependency, development of acute kidney injury (AKI), and in-hospital death. Baseline patient characteristics were recorded, including demographic variables and comorbidities.

Results
A total of 11 086 patients were included in the analysis. The study group included patients with CKD (5543 patients). Patients in the control group (5543 patients) were propensity matched for age, race, sex, and ethnicity. The primary outcome of in-hospital death or discharge to hospice was observed in 20.96% of patients with CKD compared to 11.91% of the control group with an odds ratio of 1.58 (confidence interval 1.37-1.80). ICU admission was required for 37.20% of patients in the CKD group and 21.63% of patients in the control group ($P < .001$). Ventilator dependency was found in 14.41% of patients in the CKD group and 8.59% of patients in the control group ($P < .01$). Development of AKI was seen in 5.65% of patients in the CKD group and 2.90% of patients in the control group ($P < .01$). A logistic regression model confirmed an independent association between underlying CKD and in-hospital death or discharge to hospice in patients with COVID-19.

Conclusion
Our study confirms an independent association between underlying CKD and poor outcomes among hospitalized patients with COVID-19, including in-hospital death or discharge to hospice.

Keywords
chronic renal insufficiency; chronic kidney disease; SARS-CoV-2; COVID-19; comorbidity; patient discharge; hospital mortality; critical care; coronavirus infections/mortality; risk factors

Introduction

Coronavirus disease-2019 (COVID-19) and its devastating consequences have defined health and sickness over a 2-year period (2020-2022). To date, the virus has affected 455 million people worldwide and resulted in over 6 million deaths. There is sufficient anecdotal and observational evidence to conclude that patients with comorbid illnesses have worse outcomes with COVID-19. However, based on several large population observational studies,[1-3] the Centers for Disease Control and Prevention has an updated list of comorbid illnesses, including but not limited to chronic kidney disease (CKD), heart disease, cancer, and chronic respiratory conditions, considered to be at high risk of intensive care unit (ICU) admission and death as a result of COVID-19 infection. The objective of this study was to examine the magnitude of the clinical impact the presence of CKD had on morbidity and mortality of a nationwide population of patients infected with COVID-19.

Methods

We conducted a retrospective cohort study of a large electronic inpatient data set from the HCA Healthcare electronic data warehouse, representing data from 149 hospitals in 18 states. Electronic data extraction was performed with automated interfaces. Data stripped of personal patient identifiers were stored in a secured electronic folder only accessible through institutional accounts. Institutional Review Board exemption was obtained prior to data collection.

All adult patients aged 18 or older who were admitted to HCA Healthcare hospitals between January 1, 2020, and September 1, 2020, and had a positive nasopharyngeal polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were included in the study. The study population was divided into patients in the database with CKD (study group), and patients without CKD (control group). The presence of CKD and end-stage renal disease (ESRD) was determined based on International Classification of Diseases 10th revision (ICD-10) codes of patient diagnoses present on admission to the hospital (N18.1, N.18.2 for CKD stage 1 and 2; N18.30 for CKD stage 3 unspecified; N18.31 and N18.32 for CKD stage 3a and 3b respectively; N18.4, and N18.5 for CKD stage 4 and 5 respectivey; and N18.6 for ESRD). Patients in the 2 groups were propensity score-matched for age, race, gender, and ethnicity (self-reported). Information regarding the presence of other comorbid illnesses, including essential hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (COPD), asthma, heart failure, coronary artery disease, and smoking was also based on ICD-10 codes documented on admission based on patients' medical diagnoses. Medication exposure was reported based on admission medication reconciliation performed by the admitting healthcare team.

The primary outcome of this study was in-hospital death/or discharge to hospice. Secondary outcomes included individual components of the primary outcome, ICU admission, ventilator dependency, and development of acute kidney injury (AKI) in patients with CKD stages I-V. ICD-10 codes documented in daily provider documentation were used to differentiate between CKD and AKI.

Statistical Analysis

Categorical variables were compared using the chi-square test, and continuous variables were compared using the Student's *t*-test. A propensity score was created using multivariable logistic regression analysis to match the CKD group and control group at a ratio of 1:1 on age, gender, race, and ethnicity. For the primary outcome, a multivariable logistic regression model was used, in which in-hospital death or discharge to hospice was the dependent variable, the presence of CKD was a predictor variable, and other baseline comorbidities and medications (**Table 1**) were used as covariates. A 2-tailed *P* value less than .05 was considered statistically significant. SAS 9.4 software was used in statistical analysis.

Results

A total of 11 086 patients were included in the analysis: 5543 patients in the CKD group, divided and 5543 patients in the control group. Patients in the CKD group and the control group were successfully propensity score-matched for age, race, gender, and ethnicity with no residual differences (**Table 1**). The mean age was 68, and the cohorts were 56.61% male and 43.49% female. In the CKD group, 45.26%

Table 1. Comparison of Baseline Characteristics of Admitted COVID-19-Positive Patients From the CKD Group Versus the Control Group

	CKD group n = 5543	Control group n = 5543	*P* value
Propensity Score-Matched Variables			
Age (mean, standard deviation)	68.99 (14.25)	68.99 (14.25)	.99
Gender	3138 (56.61%) Men/ 2405 (43.39%) Women	3138 (56.61%) Men/ 2405 (43.39%) Women	.99
Race	2973 (53.64%) White/1558 (28.11%) Black/929 (16.76%) Other/83 (1.50%) Asian	2973 (53.64%) White/1558 (28.11%) Black/929 (16.76%) Other/83 (1.50%) Asian	.99
Ethnicity	3889 (70.16%) Not Hispanic/1654 (29.84%) Hispanic	3889 (70.16%) Not Hispanic/1654 (29.84%) Hispanic	.99
CKD (n,%), categorized into stages according to the eGFR including ESRD			
CKD stage I (eGFR >90 ml/min)	24 (0.43%)	NA	NA
CKD stage II (eGFR 60-89 ml/min)	313 (5.65%)	NA	NA
CKD stage III (eGFR 30-59 ml/min)	2509 (45.26%)	NA	NA
CKD stage IV (eGFR 15-29 ml/min)	677 (12.21%)	NA	NA
CKD stage V (eGFR <15 ml/min)	81 (1.46%)	NA	NA
ESRD	1939 (34.98%)	NA	NA
Baseline Characteristics Not Included in Propensity Score			
Comorbidities			
Smoking	2076 (37.45%)	1700 (30.67%)	<.0001
Hypertension	3294 (59.43%)	3209 (57.89%)	.1011
Hyperlipidemia	3432 (61.92%)	2200 (39.69%)	<.0001
Diabetes	3670 (66.21%)	2094 (37.78%)	<.0001
COPD	1210 (21.83%)	738 (13.31%)	<.0001
Asthma	275 (4.96%)	280 (5.05%)	.8276
Coronary artery disease	2021 (36.46%)	900 (16.24%)	<.0001
Heart failure	2152 (38.82%)	694 (12.52%)	<.0001
Medication exposure			
ACEI	1089 (19.65%)	878 (15.84%)	<.0001
ARB	1024 (18.47%)	737 (13.30%)	<.0001
ACEI or ARB	2068 (37.31%)	1588 (28.65%)	<.0001
Beta-blockers	2490 (44.92%)	1091 (19.68%)	<.0001
Statin	2972 (53.62%)	1815 (32.74%)	<.0001
Antiplatelet	2226 (40.16%)	1269 (22.89%)	<.0001
Diuretic (thiazide and/or loop)	1614 (29.12%)	718 (12.95%)	<.0001
Anticoagulant	822 (14.83%)	464 (8.37%)	<.0001
Steroid	153 (2.76%)	155 (2.80%)	.9080

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; COPD = chronic obstructive pulmonary disease; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker

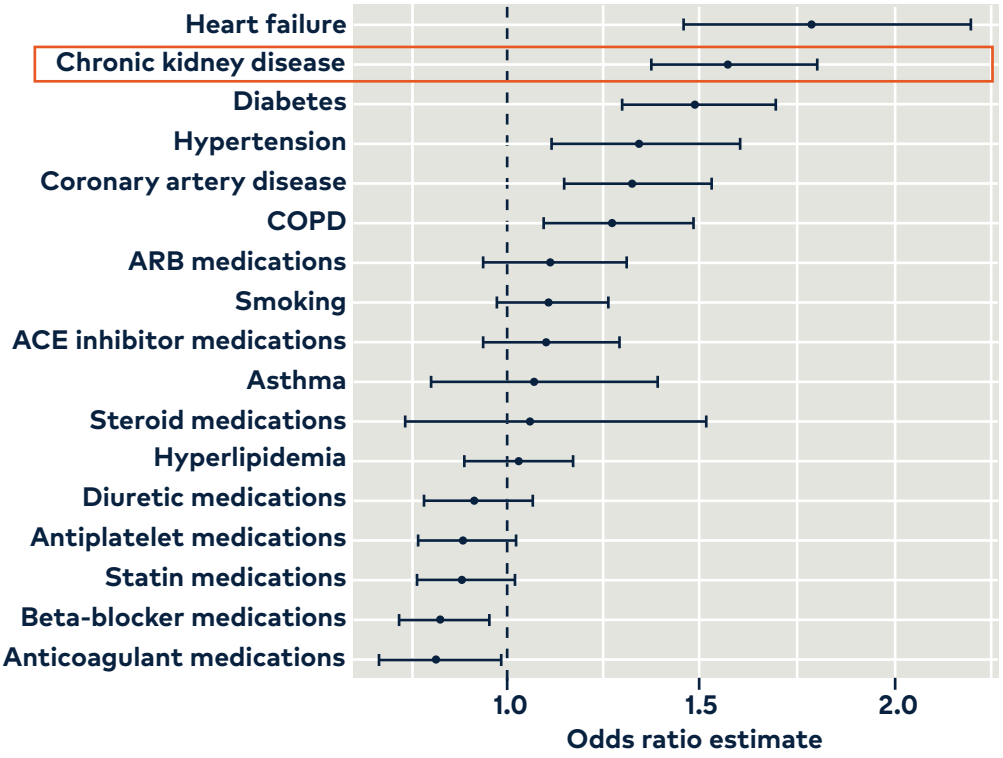

Figure 1. Odds ratios of in-hospital death or discharge to hospice due to COVID-19 in association with different comorbidities show chronic kidney disease was higher than most comorbidities studied. Abbreviations: COPD = chronic obstructive pulmonary disease; ARB = angiotensin II receptor blocker; ACE = angiotensin-converting enzyme

had CKD stage 3, and 34.98% of patients had ESRD. Not surprisingly, the presence of other co-existing comorbid illnesses was higher in the CKD group. For example, smoking, hyperlipidemia, diabetes, COPD, coronary artery disease, heart failure, and exposure to a range of medications were higher in the CKD group compared to the control group (**Table 1**).

Outcome Analysis

The primary outcome of in-hospital death or discharge to hospice was seen in 20.96% of patients with CKD, as opposed to 11.91% of the control group. Multivariate logistic regression showed that the primary outcome of in-hospital death or discharge to hospice had an odds ratio (OR) of 1.58 (95% confidence interval [CI] 1.37-1.80) in patients with CKD compared to the control group. In comparison to other comorbidities included in the model (**Figure 1**), the OR of the primary outcome in association with CKD was numerically higher than the OR of most other comorbidities, including diabetes mellitus (OR 1.44, 95% CI 1.30-1.70), hypertension (OR 1.33, 95% CI 1.12-1.64), coronary artery disease (OR 1.33, 95% CI 1.10-1.58), and COPD (OR 1.27, 95% CI 1.09-1.50). The OR for inpatient death or discharge to hospice in patients with CKD was second only to heart failure (OR 1.79, 95% CI 1.46-2.21).

In-hospital death occurred in 14.52% of the CKD group and in 7.81% of the control group ($P < .01$). ICU admission was required for 37.20% of patients with CKD and 21.63% of the control group ($P < .001$). Ventilator dependency was seen in 14.41% of patients with CKD and 8.59% of the control group ($P < .01$). Development of AKI was observed in 8.55% of patients with CKD stages I-IV, and 2.90% of patients in the control group ($P < .01$).

Discussion

Our study demonstrated that the presence of CKD was associated with an increase in in-hospital death or discharge to hospice. Of interest, the presence of CKD seems to be associated with the second highest OR of death or discharge to hospice among all comorbid conditions included in our multivariable

regression model, including diabetes, coronary artery disease, hypertension, and COPD. CKD populations were more prone to worse outcomes from COVID-19 secondary to weakened immune response and thus are susceptible to infections.[4] Hence, our findings demonstrate the significant clinical impact of the presence of CKD on COVID-19 mortality and morbidity.

Our findings are consistent with the results from other large population studies. In a 2020 prospective cohort study, in which over 20 133 patients admitted to hospitals in the United Kingdom were analyzed, 16.2% of patients were reported to have CKD on admission.[3] The presence of CKD was also associated with a hazard ratio of 1.28 for deaths from COVID-19.3. A similar New York City-based study did not show a statistically significant hazard ratio for in-hospital death from COVID-19 for patients with hypertension, diabetes, or cancer.[2] However, in this study, a glomerular filtration rate (GFR) of less than 60 was associated with a hazard ratio of 1.80 and a GFR of less than 30 was associated with a hazard ratio of 1.20.[2]

It is important to note that in large databases, small differences may reach statistical significance, though they may bear no clinical significance.[5] Therefore, it is important to consider the scientific plausibility of the findings, as well as both the absolute and relative differences in outcomes. It is important to note that in large databases small differences may reach statistical significance, though they may bear no clinical significance.[5] Therefore, it is important to consider the scientific plausibility of the findings, as well as both the absolute and relative differences in outcomes. In our study, the absolute and relative differences in our primary outcome were substantial (1164, 20.99% of the CKD group vs 660, 11.91% of the control group). This outcome was supported by modestly higher odds of in-hospital death or discharge to hospice in the CKD group (OR 1.58, 95% CI 1.37-1.80).

A relationship between developing AKI and COVID-19 has been frequently reported in the literature. Acute tubular injury is most often seen in patients with COVID-19. COVID-19 effects on the renal system are multifactorial via activation of the immune response, both locally and systemically, along with endothelial injury to initiation of the coagulation cascade and renin-angiotensin system.[6] COVID-19 can directly damage the renal compartment, especially glomeruli, but the exact mechanism of virus-induced AKI remains to be confirmed.[6] Few authors have reported cases of COVID-19-induced nephropathy, known as collapsing glomerulopathy.[6] The direct pathophysiology remains to be determined, but theoretically, COVID-19 nephropathy may share a similar mechanism as HIV-induced nephropathy via podocyte injury through disruption of autophagy along with mitochondrial dysfunction.[6] Additionally, microvascular compromise of the kidney via thrombi has been shown in COVID-19 cases via the initiation of inflammation along with SARS-CoV-2's ability to bind to the platelet angiotensin-converting enzyme 2 (ACE2) and lead to platelet aggregation and thrombosis. SARS-CoV-2's attraction toward endothelium is another mechanism of AKI as the initiation of inflammatory cascade leads to the release of tumor necrosis factor and Fas mediators, which bind directly to renal endothelial cells and cause direct injury.[6] Additionally, the promotion of the complement cascade by COVID-19 can further lead to tissue injury.[6] Elevated interleukin-6 levels in COVID-19 patients are associated with severe outcomes, such as critical care admission for acute respiratory distress syndrome and death.[6] Another example of an alteration of the immune response by COVID-19 includes suppression of interferon release, which impairs virus clearance.[6] ICU data from the United States have shown that the development of AKI is associated with increased mortality, ventilator dependency, and vasopressor support in patients with COVID-19.[7] Our study showed that the incidence of AKI was higher in patients with CKD, and this likely resulted in increased mortality as well. Renal biopsies of patients with COVID-19 have shown peritubular capillary congestion, fibrin thrombi, and renal microthrombi, which can cause poor renal perfusion.[8] Patients with CKD have decreased renal reserve and are more susceptible to hemodynamic and cytokine-mediated consequences of severe COVID-19 illness.

CKD affects both the innate and adaptive immune system responses.[7] Infection and sepsis are major causes of mortality and morbidity in patients with CKD, and infection-related mortality has been proven to be higher in

patients with reduced estimated GFR.[7] Even mild to moderately reduced kidney function is associated with a clinically meaningful increase in the risk of infection-related hospitalization.[7] CKD infection-related complications may be secondary to biochemical abnormalities, such as increased inflammatory factors, endothelial dysfunction, and enhanced coagulation.[9]

SARS-CoV-2 infects human cells by binding to the cell surface protein (ACE2) through the receptor binding domain of its spike protein.[10] The transmembrane serine protease (TMPRSS2) is required for the priming of this spike protein.[10] The ACE/ACE2 homeostasis is a critical component of several disease states including diabetes, heart failure, hypertension, and CKD, and is likely driving the morbidity and mortality in these patients.[11] ACE2 receptors are present in abundance in the kidney, and it is, therefore, expected that patients with underlying CKD may be an at-risk population.[12] The renin-angiotensin system is a complex interaction between several subtypes of angiotensin, ACE, and ACE2.[13] ACE2 activity rises along with ACE activity in healthy individuals, but the balance between ACE and ACE2 is disrupted in patients with secondary kidney disease.[14] Physiologically, abundant ACE2 expression in kidneys is thought to protect against injury, and it has been shown to slow cellular injury in experimental models.[15] ACE2 levels are depleted in patients with CKD and the internalization of the virus further depletes membrane-bound ACE2.[11] The depletion of ACE2 can also result in increased angiotensin II due to unchecked ACE activity. This increase in angiotensin II can cause increased vasoconstriction, inflammation, asalt, and water retention. The loss of renal protective function from ACE2 and subsequent increased angiotensin II may explain why patients with CKD have poor outcomes from COVID-19. Thus, it is crucial to analyze the association between COVID-19 and CKD patients. The association of ACE2 receptors with COVID-19 infection raised undue alarm at the beginning of the pandemic.[16] The proportion of patients with CKD who were taking ACE/angiotensin II receptor blockade was only 37.31%. Since about 48% of our CKD group had stage IV CKD or higher, we were unable to determine if a low proportion of ACE/ARB use was due to discontinuing these medications or presence of contraindication, such as hyperkalemia. Of note, our multivariate regression analysis revealed that neither ACE nor ARB use was associated with a worse outcome (**Figure 1**).

Limitations

This retrospective cohort study has some limitations including lack of laboratory data and the use of administrative codes to identify CKD and comorbidities. Additionally, since the CKD populations had elevated baseline serum creatinine, AKI in CKD diagnosis may have been under-reported by physicians. We also extracted electronic data, which were created in the context of clinical care, financial, and administrative management and not for research purposes. These data vary in the degree of detail and accuracy; hence, the use of ICD codes may have been varied depending on the interpretation by the medical reviewer. However, administrative codes are commonly used in the literature to identify CKD, and their specificity is high (95-99%).[17,18] Since we matched patients' groups on age, race, gender, and ethnicity only, another limitation of our study was the differences in proportions of comorbidities at baseline. However, we included all comorbidities in our logistic regression model to adjust for these differences; such an approach preserves the sample size. A final limitation to highlight, the confidence interval for our primary outcome was relatively wide, which may suggest the lack of a precise estimate.

Conclusion

In this observational retrospective study of hospitalized patients with COVID-19 from a large healthcare system, the presence of CKD was independently associated with mortality and morbidity. The presence of CKD was also associated with increased rates of in-hospital death, ICU admission, ventilator dependency, and development of AKI. Patients with kidney disease are a vulnerable population and must be prioritized when it comes to booster doses of vaccination and novel anti-viral drugs.

Conflicts of Interest

The authors declare they have no conflicts of interest.

The authors are employees of HCA Healthcare Graduate Medical Education, an organization affiliated with the journal's publisher.

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