Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19

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Abstract

Background and objectives: Coronavirus disease 2019 (COVID-19) is associated with higher risk of AKI. We aimed to describe rates and characterize predictors and health outcomes associated with AKI in a national cohort of US veterans hospitalized with COVID-19.

Design, setting, participants, & measurements: In a cohort of 5216 US veterans hospitalized with COVID-19 identified through July 23, 2020, we described changes in serum creatinine and examined predictors of AKI and the associations between AKI, health resource utilization, and death, utilizing logistic regressions. We characterized geographic and temporal variations in AKI rates and estimated variance explained by key variables utilizing Poisson regressions.

Results: In total, 1655 (32%) participants had AKI; 961 (58%), 223 (13%), and 270 (16%) met Kidney Disease Improving Global Outcomes definitions of stage 1, 2, and 3 AKI, respectively, and 201 (12%) received KRT. Eight percent of participants had AKI within 1 day of hospitalization, and 47% did not recover to baseline serum creatinine by discharge. Older age, Black race, male gender, obesity, diabetes, hypertension, and lower eGFR were significant predictors of AKI during hospitalization with COVID-19. AKI was associated with higher mechanical ventilation use (odds ratio, 6.46; 95% confidence interval, 5.52 to 7.57) and longer hospital stay (5.56 additional days; 95% confidence interval, 4.78 to 6.34). AKI was also associated with higher risk of death (odds ratio, 6.71; 95% confidence interval, 5.62 to 8.04); this association was stronger in Blacks (P value of interaction < 0.001). Hospital-level rates of AKI exhibited substantial geographic variability, ranging from 10% to 56%. Between March and July 2020, AKI rates declined from 40% to 27%; proportions of AKI stage 3 and AKI requiring KRT decreased from 44% to 17%. Both geographic and temporal variabilities were predominately explained by percentages of Blacks (31% and 49%, respectively).

Conclusions: AKI is common during hospitalization with COVID-19 and associated with higher risk of health care resource utilization and death. Nearly half of patients with AKI did not recover to baseline by discharge. Substantial geographic variation and temporal decline in rates and severity of AKI were observed.

Introduction

Coronavirus disease 2019 (COVID-19) is associated with higher risk of hospitalization and mortality (1,2). The illness is characterized by a systemic inflammatory response and higher risk of respiratory failure and AKI (3,4). Several reports from China, Europe, and the United States described characteristics and outcomes of AKI among hospitalized patients with COVID-19 (5–8). Reports of COVID-19–associated AKI in the United States have so far been limited to a few studies from regional health systems. The emerging evidence suggests variable rates of AKI and substantial geographic heterogeneity. More evidence on characteristics and outcomes of AKI from various health systems representing different populations is needed to arm clinicians, hospital administrators, public health officials, and policy makers with a deeper and more comprehensive understanding of COVID-19–associated AKI to optimize management of this disease and its complications.

In this work, we built a national cohort of 5216 US veterans hospitalized with COVID-19, and we aimed to describe rates of AKI, characterize the demographic and health characteristics associated with AKI, and evaluate health outcomes of COVID-19–associated AKI. The findings will add to our evolving knowledge of COVID-19 and its kidney manifestations, and they will inform care of patients with COVID-19.

Materials and Methods

Cohort

We identified users of the Department of Veterans Affairs (VA) health care system with at least one laboratory-confirmed COVID-19 test between February 1, 2020 and July 23, 2020 (n = 29,071), selecting those with a hospital admission between 5 days before and 30 days after a positive test (n = 6763). The first record of COVID-19 was March 2nd. We excluded those with a history of ESKD and those with no...
measure of outpatient serum creatinine in the 7–365 days prior to hospitalization, resulting in an analytic cohort of 5216 veterans (Supplemental Figure 1). Participants were followed through July 30, 2020. Further details are included in Supplemental Material.

Data Sources
Data were obtained from the VA Corporate Data Warehouse (9–16). Participants with COVID-19 were identified using the VA COVID-19 Shared Data Resource (17). The 2015 Area Deprivation Index (ADI) was used as a contextual composite measure of a geographic location’s socioeconomic disadvantages (18). Further information on data sources may be found in Supplemental Material.

AKI
AKI was identified and staged using the serum creatinine-based Kidney Disease Improving Global Outcomes (KDIGO) guidelines (19). A baseline serum creatinine was defined as the median outpatient serum creatinine in the 7–365 days prior to hospitalization. Receipt of KRT was identified by diagnostic and procedure codes, which may be found in Supplemental Table 1A (17). In analyses of AKI severity, we included stages 1, 2, and 3 AKI and AKI receiving KRT. We investigated the percentage of those with an AKI within the first day of hospitalization. We investigated, in those who were discharged, characteristics of the AKI by severity, including time from hospitalization until first serum creatinine that met a KDIGO definition of AKI, peak of the serum creatinine trajectory, timing until the peak serum creatinine value, discharge serum creatinine, percentage with a discharge serum creatinine higher than baseline, and percentage with a discharge serum creatinine >0.3 mg/dl above baseline. Further details are included in Supplemental Material.

Outcomes
Main outcomes of the study included all-cause mortality, discharge, and need for mechanical ventilation. We also investigated length of stay in all participants, those who died, those who were discharged, and those still in the hospital. Further details are included in Supplemental Material and Supplemental Table 1B.

Participant Characteristics
Characteristics reported include demographics, hospitalization characteristics, comorbidities, laboratory tests and vital signs, and medication history (20–25). Further details may be found in Supplemental Material and Supplemental Table 1C.

Statistical Analyses
Characteristics of the cohort overall and by AKI status are reported. We additionally report characteristics by race. We plot serum creatinine trajectories by severity over 14 and 30 days.

We assessed predictors of AKI during a COVID-19 hospitalization using a logistic regression model (20,26–28). We estimated the unadjusted associations of predictors of prehospitalization characteristics known to be associated with risk of AKI and then constructed a multivariable model using a variable selection algorithm.

We additionally conducted a proportional odds regression to assess predictors of having a more severe AKI. Further details on additional complimentary analyses are included in Supplemental Material (29,30). The adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported.

Clinical outcomes overall, by AKI status, and by AKI severity are presented, and differences between those with and without AKI and by severity were assessed using t tests and linear regressions. The associations between AKI and AKI severity with mechanical ventilation during hospitalization and length of stay were assessed using logistic and linear regressions, respectively. We assessed the risk of mortality by AKI status and conducted formal interaction analyses using adjusted logistic regression (31).

We furthermore assessed risk of mortality by AKI severity. We present results in a forest plot. Further details are included in Supplemental Material.

We identiﬁed and staged using the serum creatinine-based Kidney Disease Improving Global Outcomes (KDIGO) guidelines (19). A baseline serum creatinine was defined as the median outpatient serum creatinine in the 7–365 days prior to hospitalization. Receipt of KRT was identified by diagnostic and procedure codes, which may be found in Supplemental Table 1A (17). In analyses of AKI severity, we included stages 1, 2, and 3 AKI and AKI receiving KRT. We investigated the percentage of those with an AKI within the first day of hospitalization. We investigated, in those who were discharged, characteristics of the AKI by severity, including time from hospitalization until first serum creatinine that met a KDIGO definition of AKI, peak of the serum creatinine trajectory, timing until the peak serum creatinine value, discharge serum creatinine, percentage with a discharge serum creatinine higher than baseline, and percentage with a discharge serum creatinine >0.3 mg/dl above baseline. Further details are included in Supplemental Material.

All statistical tests were two sided, where a $P<0.05$ or a 95% CI that did not contain unity was considered statistically significant. No imputation was done. The study was approved by the Institutional Review Board of the VA St. Louis Health Care System, St. Louis, Missouri.

Results
Characteristics of Hospitalized Patients with Coronavirus Disease 2019 with and without AKI

We identiﬁed 5216 hospitalized US veterans with COVID-19 and no prior history of ESKD between February 1, 2020 and July 23, 2020. Demographic and health characteristics are reported in Table 1 for the overall cohort and by AKI status. Of these patients, 4095 (79%) had been discharged, 832 (16%) died, and 289 (6%) were still hospitalized on July 30, 2020. Characteristics of the cohort by race are provided in Supplemental Table 2. Characteristics of those excluded due to a missing baseline serum creatinine are included in Supplemental Table 3.

Of those with a COVID-19 hospitalization, 1655 (32%) had met KDIGO serum creatinine deﬁnitions of AKI by date of last record (July 30, 2020) (Table 1). Compared with those who had not experienced an AKI, those who experienced AKI were older; had a higher proportion of Black participants; and had a higher proportion of participants with a history of cardiovascular disease, diabetes mellitus type 2, and hypertension, as well as a lower baseline eGFR. Compared with those with no AKI, levels of baseline serum creatinine, BUN, and white blood cell count were higher in those who experienced an AKI, whereas albumin, hemoglobin, platelet count, and serum bicarbonate were lower. Use of angiotensin-converting enzyme...
inhibitors/angiotensin II receptor blockers and diuretics within the 30 days before hospitalization was higher in those with AKI compared with those without AKI (Table 1). AKI was associated with higher rates of receipt of care in an intensive care unit (24% versus 51%) and mechanical ventilation (8% versus 35%).

Table 1. Demographic and health characteristics of the overall cohort and by AKI status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall, n=5216</th>
<th>No AKI, n=3561 (68%)</th>
<th>AKI, n=1655 (32%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), yr</td>
<td>70 (61–76)</td>
<td>69 (59–76)</td>
<td>72 (64–77)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2615 (50)</td>
<td>1924 (54)</td>
<td>691 (42)</td>
</tr>
<tr>
<td>Black</td>
<td>2308 (44)</td>
<td>1427 (40)</td>
<td>881 (53)</td>
</tr>
<tr>
<td>Other</td>
<td>293 (6)</td>
<td>210 (6)</td>
<td>83 (5)</td>
</tr>
<tr>
<td>Sex, no. (%), men</td>
<td>4908 (94)</td>
<td>3300 (93)</td>
<td>1608 (97)</td>
</tr>
<tr>
<td>ADI, median (IQR)</td>
<td>52 (40–60)</td>
<td>52 (40–60)</td>
<td>52 (39–61)</td>
</tr>
<tr>
<td>BMI category, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight/normal</td>
<td>791 (15)</td>
<td>576 (16)</td>
<td>215 (13)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1746 (34)</td>
<td>1214 (34)</td>
<td>532 (32)</td>
</tr>
<tr>
<td>Obese</td>
<td>2679 (51)</td>
<td>1771 (50)</td>
<td>908 (55)</td>
</tr>
<tr>
<td>Smoking status, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>2893 (56)</td>
<td>2019 (57)</td>
<td>874 (53)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1490 (29)</td>
<td>944 (27)</td>
<td>546 (33)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>833 (16)</td>
<td>598 (17)</td>
<td>235 (14)</td>
</tr>
<tr>
<td>Hospital characteristics, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>1693 (33)</td>
<td>855 (24)</td>
<td>838 (51)</td>
</tr>
<tr>
<td>Ventilator</td>
<td>863 (17)</td>
<td>278 (8)</td>
<td>585 (35)</td>
</tr>
<tr>
<td>Comorbidities, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>799 (15)</td>
<td>529 (15)</td>
<td>270 (16)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1588 (30)</td>
<td>1014 (29)</td>
<td>574 (35)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>726 (14)</td>
<td>475 (13)</td>
<td>251 (15)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1302 (25)</td>
<td>865 (24)</td>
<td>437 (26)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>2679 (51)</td>
<td>1771 (50)</td>
<td>908 (55)</td>
</tr>
<tr>
<td>Dementia</td>
<td>657 (13)</td>
<td>461 (13)</td>
<td>196 (12)</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>2537 (49)</td>
<td>1584 (45)</td>
<td>953 (58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3985 (76)</td>
<td>2569 (72)</td>
<td>1416 (86)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>202 (4)</td>
<td>131 (4)</td>
<td>71 (4)</td>
</tr>
<tr>
<td>Charlson comorbidity score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4 (2.4)</td>
<td>2.3 (2.4)</td>
<td>2.7 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Laboratory tests and vital signs, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dl, n=5063</td>
<td>3.5 (3.1–3.9)</td>
<td>3.5 (3.1–3.9)</td>
<td>3.4 (3.0–3.8)</td>
</tr>
<tr>
<td>Baseline eGFR, ml/min per 1.73 m²</td>
<td>73 (57–89)</td>
<td>77 (62–91)</td>
<td>70 (58–81)</td>
</tr>
<tr>
<td>Baseline serum creatinine, mg/dl</td>
<td>1.1 (0.9–1.3)</td>
<td>1.1 (0.9–1.2)</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td>BP (diastolic), mm Hg, n=5214</td>
<td>76 (71–81)</td>
<td>76 (71–82)</td>
<td>75 (70–81)</td>
</tr>
<tr>
<td>BP (systolic), mm Hg, n=5214</td>
<td>133 (124–142)</td>
<td>132 (123–141)</td>
<td>134 (124–144)</td>
</tr>
<tr>
<td>BUN, mg/dl, n=5154</td>
<td>18 (13–28)</td>
<td>16 (12–21)</td>
<td>31 (20–48)</td>
</tr>
<tr>
<td>Hemoglobin, g/dl, n=5070</td>
<td>13.4 (12.0–14.5)</td>
<td>13.4 (12.0–14.5)</td>
<td>13.1 (11.3–14.5)</td>
</tr>
<tr>
<td>Lymphocytes, %, n=4805</td>
<td>16 (11–24)</td>
<td>18 (11–25)</td>
<td>13 (8–20)</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/L, n=5173</td>
<td>194 (151–253)</td>
<td>197 (153–255)</td>
<td>188 (146–250)</td>
</tr>
<tr>
<td>Serum bicarbonate, mEq/L, n=5212</td>
<td>24.0 (22.0–26.0)</td>
<td>25.0 (22.6–27.0)</td>
<td>23.0 (20.0–25.0)</td>
</tr>
<tr>
<td>White blood cell count, ×10⁹/L, n=5041</td>
<td>6.3 (4.8–8.4)</td>
<td>6.1 (4.6–8.0)</td>
<td>6.7 (5.1–9.1)</td>
</tr>
<tr>
<td>Medications, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>1718 (33)</td>
<td>1048 (29)</td>
<td>670 (41)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>86 (2)</td>
<td>58 (2)</td>
<td>28 (2)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>415 (8)</td>
<td>264 (7)</td>
<td>151 (9)</td>
</tr>
<tr>
<td>Antiviral</td>
<td>68 (1)</td>
<td>48 (1)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>913 (18)</td>
<td>589 (17)</td>
<td>324 (20)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1546 (30)</td>
<td>955 (27)</td>
<td>591 (36)</td>
</tr>
<tr>
<td>Chemotherapy agents</td>
<td>35 (0.7)</td>
<td>21 (0.6)</td>
<td>14 (0.8)</td>
</tr>
<tr>
<td>Diuretics: loop</td>
<td>629 (12)</td>
<td>374 (11)</td>
<td>255 (15)</td>
</tr>
<tr>
<td>Diuretics: MRA</td>
<td>214 (4)</td>
<td>115 (3)</td>
<td>99 (6)</td>
</tr>
<tr>
<td>Diuretics: thiazide/other</td>
<td>808 (16)</td>
<td>466 (13)</td>
<td>342 (21)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>27 (0.5)</td>
<td>12 (0.3)</td>
<td>15 (0.9)</td>
</tr>
<tr>
<td>NSAID</td>
<td>656 (13)</td>
<td>465 (13)</td>
<td>191 (12)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>1213 (23)</td>
<td>832 (23)</td>
<td>381 (23)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; ADI, Area Deprivation Index; BMI, body mass index; ICU, intensive care unit; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug.

*ADI is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of zero to 100.

Characteristics of AKI in Patients Hospitalized with Coronavirus Disease 2019

Of the 1655 patients who had AKI, 961 (58%), 223 (13%), and 270 (16%) met KDIGO definitions of stage 1, 2, and 3 AKI, respectively (Table 2); 201 (12%) patients with AKI received KRT. Most participants (80%) with AKI experienced it (met the
definition of AKI) within the first day of hospitalization (Table 2, Supplemental Figure 2). Characteristics of serum creatinine trajectories by AKI stage among all participants and among those who were discharged alive are presented in Table 2. Among those who were discharged who had received KRT, 12 (20%) had a record of continuing to receive KRT after discharge. Discharge serum creatinine was higher than pre-hospitalization baseline serum creatinine in 47% of participants with AKI; mean discharge serum creatinine was higher than mean baseline in AKI stages 2 and 3 and in those who received KRT (Table 2). Smoothed plots of 14- and 30-day serum creatinine trajectories by AKI stage among all participants and characteristics of serum creatine stratified by AKI stage (Table 2). Characteristics of serum creatine stratified by AKI stage

<table>
<thead>
<tr>
<th>Table 2. Characteristics of serum creatine stratified by AKI stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics among All Patients with AKI</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Baseline serum creatinine</strong></td>
</tr>
<tr>
<td>Mean (SD), mg/dl</td>
</tr>
<tr>
<td>Median (IQR), mg/dl</td>
</tr>
<tr>
<td>AKI within 1 d of hospitalization, no. (%)</td>
</tr>
<tr>
<td><strong>Characteristics among discharged patients</strong> with AKI</td>
</tr>
<tr>
<td>Baseline serum creatinine</td>
</tr>
<tr>
<td>Mean (SD), mg/dl</td>
</tr>
<tr>
<td>Median (IQR), mg/dl</td>
</tr>
<tr>
<td>Peak serum creatinine</td>
</tr>
<tr>
<td>Mean (SD), mg/dl</td>
</tr>
<tr>
<td>Median (IQR), mg/dl</td>
</tr>
<tr>
<td><strong>Time to peak serum creatinine</strong></td>
</tr>
<tr>
<td>Mean (SD), d</td>
</tr>
<tr>
<td>Median (IQR), d</td>
</tr>
<tr>
<td><strong>Discharge serum creatinine</strong></td>
</tr>
<tr>
<td>Mean (SD), mg/dl</td>
</tr>
<tr>
<td>Median (IQR), mg/dl</td>
</tr>
<tr>
<td>Discharge serum creatinine &gt; baseline, no. (%)</td>
</tr>
<tr>
<td>Discharge serum creatinine &gt; baseline +0.3 mg/dl, no. (%)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
aExcluding those patients who died and those still under treatment.
bIn those who received KRT, serum creatinine was censored at initiation of dialysis.

definition of AKI) within the first day of hospitalization (Table 2, Supplemental Figure 2). Characteristics of serum creatinine trajectories by AKI stage among all participants and among those who were discharged alive are presented in Table 2. Among those who were discharged who had received KRT, 12 (20%) had a record of continuing to receive KRT after discharge. Discharge serum creatinine was higher than pre-hospitalization baseline serum creatinine in 47% of participants with AKI; mean discharge serum creatinine was higher than mean baseline in AKI stages 2 and 3 and in those who received KRT (Table 2). Smoothed plots of 14- and 30-day serum creatinine trajectories by AKI severity among all those discharged alive are provided in Figure 1, A and B, respectively.

**Predictors of an AKI during Hospitalization with Coronavirus Disease 2019**

Unadjusted associations between predictors and risk of AKI during a COVID-19 hospitalization are presented in Table 3 and Supplemental Table 4. In adjusted multivariable models, older age, Black race, male gender, obesity, diabetes mellitus type 2, and hypertension were associated with having an AKI and having a more severe AKI in those with a COVID-19 hospitalization (Table 3). Diuretic and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use was associated with higher risk of any AKI and having a more severe AKI (Table 3). There was a higher risk of AKI and AKI severity with decreasing eGFR category (Table 3). Results of multivariable models that included all prespecified potential predictors (Supplemental Table 4) were consistent (Table 3). A one–interquartile range higher

Charlson comorbidity score (3) was associated with higher risk of AKI and AKI severity (OR, 1.12; 95% CI, 1.04 to 1.21 and OR, 1.11; 95% CI, 1.03 to 1.20, respectively) (Supplemental Table 4). Results were consistent in adjusted analyses considering the three-point composite outcome of AKI stage 3, AKI receiving KRT, or death, and separately, the two-point composite outcome of AKI receiving KRT or death (Supplemental Table 5).

**Outcomes in Coronavirus Disease 2019 Hospitalization with an AKI**

We observed 832 (16%) deaths in the overall cohort; 559 (34%) and 273 (8%) were in those with and without AKI, respectively (Table 4). There was a higher mortality rate by AKI severity; 184 (19%), 86 (39%), 160 (59%), and 129 (64%) deaths occurred in AKI stages 1, 2, and 3 and AKI receiving KRT, respectively (Table 4). Ventilator use was more frequent in those with AKI compared with those without AKI (35% versus 8%; P<0.001), and it was higher by AKI stage, with 18%, 43%, 57%, and 82% in stages 1, 2, and 3 and in those receiving KRT, respectively (P value for trend <0.001). Compared with those with no AKI, in unadjusted models, those with an AKI had 6.46 (95% CI, 5.52 to 7.57) times the odds of ventilator use, with 2.59 (95% CI, 2.11 to 3.18), 8.76 (95% CI, 6.53 to 11.73), 15.44 (95% CI, 11.80 to 20.26), and 52.34 (95% CI, 36.31 to 77.34) times the odds in AKI stages 1, 2, and 3 and receiving KRT, respectively.

Length of hospital stay was longer among those with AKI compared with those without (median 10 versus 5 days; P<0.001), and it was higher with AKI severity, with
median lengths of stay of 8, 11, 10, and 17 days in AKI stages 1, 2, and 3 and in those receiving KRT, respectively \((P\) value for trend <0.001) (Table 4). Compared with no AKI, in unadjusted models, having an AKI was associated with an additional 5.56 (95% CI, 4.78 to 6.34) days in the hospital, whereas AKI stages 1, 2, and 3 and receiving KRT were associated with 2.73 (95% CI, 1.79 to 3.66), 8.32 (95% CI, 6.54 to 10.11), 5.84 (95% CI, 4.21 to 7.46), and 15.71 (95% CI, 13.84 to 17.58) additional days in the hospital, respectively. Similar patterns in median length of stay were observed in subgroup analyses of those who died, were discharged, or were still in the hospital (Table 4), and in those who were discharged or died (Supplemental Table 6).

### Association between AKI during a Coronavirus Disease 2019 Hospitalization and Risk of Death

Compared with those without AKI, those with an AKI during a COVID-19 hospitalization had 6.71 (95% CI, 5.62 to 8.04) times higher odds of death in adjusted models.

Figure 1. | Trajectories of serum creatinine among a cohort of U.S. veterans hospitalized with coronavirus disease 2019 who were discharged alive. (A) Fourteen and (B) 30 days. Baseline serum creatinine is included at time −1. Trajectories are colored by AKI status and severity. In those who received KRT, the serum creatinine trajectory was censored at the time of KRT. Bands represent the 95% confidence intervals.
tion analyses showed that Black race strengthened the association between AKI and death on the multiplicative scale ($P=0.003$), whereas age above the median attenuated the association ($P<0.001$) (Figure 2A); diabetes, hypertension, obesity status, and eGFR range showed no evidence of

(Supplemental Table 7). Results were consistent in survival analyses when AKI was treated as a time-varying variable (hazard ratio, 5.82; 95% CI, 4.98 to 6.80). Formal interaction analyses showed that Black race strengthened the association between AKI and death on the multiplicative scale ($P=0.003$), whereas age above the median attenuated the association ($P<0.001$) (Figure 2A); diabetes, hypertension, obesity status, and eGFR range showed no evidence of

### Table 3. Demographic and health characteristics associated with AKI and AKI severity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Any AKI Odds Ratio</th>
<th>AKI Severity Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Age in 10 yr</td>
<td>1.24 (1.18 to 1.30)</td>
<td>1.09 (1.03 to 1.16)</td>
</tr>
<tr>
<td>Sex, reference = women</td>
<td>2.71 (1.99 to 3.76)</td>
<td>2.14 (1.54 to 3.03)</td>
</tr>
<tr>
<td>Race, reference = White</td>
<td>1.72 (1.52 to 1.94)</td>
<td>1.93 (1.69 to 2.20)</td>
</tr>
<tr>
<td>BMI category, reference = underweight/normal</td>
<td>1.10 (0.84 to 1.43)</td>
<td>1.14 (0.85 to 1.51)</td>
</tr>
<tr>
<td>Smoking status, reference = never smoked</td>
<td>1.17 (0.97 to 1.42)</td>
<td>1.17 (0.96 to 1.43)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.33 (1.18 to 1.51)</td>
<td>0.86 (0.75 to 1.00)</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>1.69 (1.51 to 1.91)</td>
<td>1.27 (1.11 to 1.45)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.29 (1.96 to 2.68)</td>
<td>1.31 (1.10 to 1.57)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.63 (1.44 to 1.84)</td>
<td>1.22 (1.07 to 1.41)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>1.85 (1.64 to 2.10)</td>
<td>1.32 (1.14 to 1.52)</td>
</tr>
<tr>
<td>Diureticsb</td>
<td>1.25 (1.02 to 1.54)</td>
<td>0.96 (0.76 to 1.21)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>2.71 (1.27 to 5.91)</td>
<td>2.19 (0.97 to 5.03)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.34 (1.17 to 1.52)</td>
<td>1.24 (1.07 to 1.42)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.91 (0.76 to 1.08)</td>
<td>1.06 (0.88 to 1.27)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>1.52 (1.34 to 1.72)</td>
<td>1.05 (0.90 to 1.22)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1.23 (1.06 to 1.43)</td>
<td>0.94 (0.79 to 1.11)</td>
</tr>
<tr>
<td>eGFR category, reference = eGFR&gt;90 ml/min per 1.73 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61–90 ml/min per 1.73 m²</td>
<td>1.43 (1.21 to 1.69)</td>
<td>1.37 (1.14 to 1.64)</td>
</tr>
<tr>
<td>46–60 ml/min per 1.73 m²</td>
<td>2.97 (2.47 to 3.63)</td>
<td>2.60 (2.10 to 3.23)</td>
</tr>
<tr>
<td>30–45 ml/min per 1.73 m²</td>
<td>4.16 (3.32 to 5.23)</td>
<td>3.33 (2.57 to 4.31)</td>
</tr>
<tr>
<td>&lt;30 ml/min per 1.73 m²</td>
<td>8.36 (1.82 to 36.6)</td>
<td>7.28</td>
</tr>
<tr>
<td>(5.82 to 12.36)</td>
<td>(4.91 to 10.95)</td>
<td>(5.93 to 11.32)</td>
</tr>
</tbody>
</table>

Adjusted estimates adjust for covariates listed in the table. BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

aSeverity is defined by increasing stage of AKI (no AKI; stage 1, 2, or 3 AKI, and AKI receiving KRT), where the odds ratio represents the odds of having a more severe AKI compared with a less severe one.

bIncludes loop, mineralocorticoid receptor antagonists, and thiazides/other diuretics.

### Table 4. Outcomes in the overall cohort of hospitalized patients with coronavirus disease 2019 and by AKI stage

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>AKI Status</th>
<th>AKI Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No AKI</td>
<td>AKI</td>
</tr>
<tr>
<td>Mortality, no. (%)</td>
<td>832 (16)</td>
<td>273 (8)</td>
<td>559 (34)</td>
</tr>
<tr>
<td>Ventilator, no. (%)</td>
<td>863 (17)</td>
<td>278 (8)</td>
<td>585 (35)</td>
</tr>
<tr>
<td>Discharge, no. (%)</td>
<td>4095 (79)</td>
<td>3075 (86)</td>
<td>1020 (62)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among all patients</td>
<td>7 (3–13)</td>
<td>5 (2–11)</td>
<td>10 (5–18)</td>
</tr>
<tr>
<td>Among those who died</td>
<td>10 (5–16)</td>
<td>8 (4–14)</td>
<td>11 (6–17)</td>
</tr>
<tr>
<td>Among those discharged</td>
<td>6 (3–11)</td>
<td>5 (2–9)</td>
<td>9 (4–19)</td>
</tr>
<tr>
<td>Among those still in hospital</td>
<td>14 (7–28)</td>
<td>13 (7–27)</td>
<td>16 (8–30)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
modifying the association between AKI and death (Supplemental Table 7). In adjusted analyses by AKI stage (Figure 2B), there was a graded increase in risk of death by increasing AKI severity: risk of death in stage 1 (OR, 2.97; 95% CI, 2.38 to 3.71), stage 2 (OR, 8.41; 95% CI, 6.07 to 11.63), stage 3 (OR, 25.19; 95% CI, 18.43 to 34.65), and AKI receiving KRT (OR, 42.68; 95% CI, 29.74 to 61.88) (Supplemental Table 8).

National Geographic and Temporal Variability in Rates of AKI among Hospitalized Patients with Coronavirus Disease 2019

A map of the geographic distribution of hospitalized patients with COVID-19 showed that the majority of patients with AKI were in Arizona, California, Florida, Illinois, Indiana, Michigan, New Jersey, New York, and Texas (Figure 3). Substantial geographic variability in hospital-level rates of AKI was observed (Figure 3), with
rates ranging from 10% to 56% (median, 31%; interquartile range, 24%–36%). Analyses of the national variability in AKI rates between hospital systems suggested that the COVID-19 hospitalized population percentage of Black race explained 31% of differences in rates, followed by mean age (11%), mean ADI (10%), rates of obesity (9%), rates of diabetes (9%), rates of hypertension (9%), and CKD (9%); altogether, these variables explained 86% of the total observed geographic variance in AKI rates.

Rates of AKI declined over time (from 40% in March to 27% in July) (Figure 4A). Among those with AKI, there was also a shift in the distribution of AKI severity, with increase in the proportion of stage 1 AKI (from 42% in March to 72% in July) and decline in the proportion of AKI stage 3 and AKI requiring KRT (from 44% in March to 17% in July) (Figure 4, B and C, Supplemental Table 9). The temporal variability in AKI rates was explained by percentage of Black race (49%), followed by percentage with diabetes (10%), mean age (7%), percentage with hypertension (6%), percentage obese (1%), and mean ADI (1%); percentage with CKD did not explain any observed variance independent of the other participant characteristics. Altogether, these variables explained 74% of the total observed temporal variance in AKI rates.

Discussion

In this national cohort of 5216 US veterans hospitalized for COVID-19, 1655 (32%) had AKI, 201 (12%) of whom received KRT. Most (80%) experienced AKI within 1 day of hospitalization, and 47% did not recover to their baseline serum creatinine value at discharge. Older age, male gender, Black race, obesity, hypertension, diabetes, and lower eGFR category were significant predictors of AKI.
Figure 4. | Rates of AKI in COVID-19 hospitalized veterans by calendar month. (A) Rates of AKI in COVID-19 hospitalizations. (B) Rates of AKI in COVID-19 hospitalizations by AKI stage. (C) Proportions of AKI stage among all patients with AKI during a COVID-19 hospitalization. Error bars represent 95% CIs.
during hospitalization with COVID-19. Compared with those without AKI, those with AKI exhibited greater need for mechanical ventilation, had longer hospital stays, and had higher mortality. Substantial geographic variability in hospital-level rates of AKI was observed. Between March and July 2020, rates of AKI declined, and the proportions of stage 3 AKI and AKI requiring KRT declined. Both spatial and temporal variations were predominantly explained by Black race.

The finding that among those hospitalized with COVID-19, 32% had AKI is generally consistent with findings in prior studies in the United States (which ranged from 28% to 43%) (6,7,33–38). In our cohort, 12% received KRT—generally consistent with the reported range (5%–31%) from several regional health systems in the United States (6,7,35,38). The observation that 80% of people experienced AKI within the first day of hospitalization suggests that the onset of kidney injury likely preceded hospitalization in most patients. We also note that a sizable proportion (47%) experienced partial or incomplete recovery—which highlights the need for careful monitoring and post-AKI care to reduce the risk of AKI recurrence and mitigate risk of long-term adverse consequences, including potential development or progression of CKD (39,40).

In our analyses, we characterized predictors of AKI; we note the strong graded relationship between decreased eGFR category and odds of AKI, suggesting that those with lower baseline eGFR are at higher risk of AKI during hospitalization with COVID-19. Compared with those without AKI, more people with AKI required mechanical ventilation, had longer hospital stays, and had higher risk of death; these rates may be used to help inform ongoing efforts to manage the current wave and to optimize planning and resource allocation for future waves of this global pandemic (41).

We noted substantial national geographic heterogeneity in rates of AKI. Rates of AKI also decreased as the pandemic unfolded (from 40% in March 2020 to 27% in July 2020) and exhibited a shift in the distribution of AKI severity, with higher proportion of milder AKI (stage 1) and reduced proportions of severe AKI (AKI stage 3 and AKI requiring KRT). Much of the geographic and temporal variance was explained by the changing landscape of racial makeup (differences in the percentage of Blacks), age, and comorbidity burden of hospitalized patients with COVID-19. The observation that the geographic and temporal variations are explained by race and comorbidities might also explain why COVID-19–associated AKI and related adverse outcomes seem to be much worse in the United States compared with East Asian countries (China and others), which have different underlying population characteristics (10,42,43). As the pandemic continues to rage unabated in the United States, characteristics of people infected with COVID-19 will likely continue to change, and as a result, further shifts in the epidemiology of COVID-19–associated AKI are to be anticipated. Our work sheds light on some key explanatory variables, which may contribute to spatiotemporal heterogeneity in the disease.

The COVID-19 global pandemic is exacting human, economic, and societal tolls unseen in decades, and it has exposed bare the world’s deepest inequities. Our results suggest that Black race exhibited a strong association with AKI (1.9-fold) and strengthened (by effect modification) the association between AKI and the risk of death. Our analyses also suggest that both spatial and temporal variations in AKI rates were predominantly explained by the percentage of Black race. The observations are made in the VA health system—the largest nationally integrated health system in the United States that is designed to provide equitable access and reduce care variations and has repeatedly delivered high-quality care (44). Differences in risk observed on the basis of race may reflect differences in exposure to upstream factors (likely social, economic, environmental, and other stressors) that may heighten the risk of AKI and its adverse consequences. These observations should also be considered along with findings in our cohort (and in other studies of hospitalized patients with COVID-19) that did not suggest higher adjusted overall risk of mortality in Blacks compared with Whites (45,46). The findings illustrate the complex interplay of the various factors shaping health outcomes. A better and deeper understanding of drivers of health disparities (in AKI, in COVID-19, and in health outcomes more broadly) is needed, and identification of actionable solutions will help move us closer to health equity.

This is an observational cohort study with some limitations. We relied on electronic health record data to characterize the rates of AKI; while we used validated definitions to capture AKI and other relevant parameters, inaccurate measurements of variables and misclassification bias may not be completely eliminated. Our datasets did not include information on urine output or other urinary findings or on inflammatory markers, nor did they include data on the etiology or the histopathologic features of AKI or dose and type of dialysis modality. Our data did not contain individual measures of socioeconomic status. Our multivariable analyses were adjusted for available relevant covariates, but we cannot completely exclude the possibility of residual confounding (i.e., the presence of unknown or unmeasured covariates). We built a cohort of US veterans hospitalized for COVID-19, which included mostly older White men with access to the VA’s nationally integrated health care system, and our results may not be generalizable to broader populations. Our cohort selection criteria may have resulted in inclusion of participants with COVID-19 who may have been hospitalized for non–COVID-19–related conditions. Finally, as this pandemic continues to evolve, our understanding of the epidemiology and characteristics of AKI in COVID-19 will continue to evolve.

Strengths of this study include the use of data from a national integrated health care delivery system that spans the entire United States. This facilitated obtaining more complete health history, including baseline kidney function and a comprehensive characterization of comorbidities. The national cohort also allowed the examination of geographic difference in rates of AKI at the health system level.

In sum, our results showed that AKI was common in hospitalized patients with COVID-19. Most AKI was encountered within the first 24 hours of hospitalization, and most patients were discharged with partial or incomplete recovery of serum creatinine. In hospitalized patients with COVID-19, Black race was associated with higher risk of AKI and strengthened the association
between AKI and the risk of death. AKI rates exhibited substantial geographic variability and temporal decline; both were predominantly explained by Black race (i.e., the societal, economic, environmental, and other disparities associated with race) and to a lesser—but measurable—extent, age and comorbidity burden. Our results may help inform efforts to optimize the ongoing management of this global pandemic and planning for long-term care needs of convalescent patients with COVID-19.

Disclosures

All authors have nothing to disclose.

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Z. Al-Aly, B. Bowe, M. Cai, and Y. Xie contributed to the development of the study concept and design; B. Bowe, M. Cai, and Y. Xie contributed to data acquisition; Z. Al-Aly, B. Bowe, M. Cai, A.K. Gibson, and Y. Xie contributed to data analysis and interpretation; B. Bowe, M. Cai, and Y. Xie contributed to statistical analysis; Z. Al-Aly, B. Bowe, and M. Cai drafted the manuscript; Z. Al-Aly, B. Bowe, M. Cai, A.K. Gibson, G. Maddukuri, and Y. Xie contributed critical revision of the manuscript; Z. Al-Aly provided administrative, technical, and material support; Z. Al-Aly contributed supervision and mentorship; all authors contributed important intellectual content during manuscript drafting or revision and accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved; Z. Al-Aly takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained; and all authors approved the final version of the report.

Data Sharing Statement

Data are not publicly available. All data are available by request from the US Department of Veterans Affairs.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09610620/-/DCSupplemental.

Supplemental Figure 1. Flow chart diagram of cohort participant inclusion.

Supplemental Figure 2. Histogram of the time to AKI during the first 2 weeks of follow-up.


Supplemental Table 1. Diagnostic and procedure codes for (A) dialysis, (B) ventilator use, and (C) comorbidities.

Supplemental Table 2. Demographic and health characteristics of the overall cohort and by race.

Supplemental Table 3. Characteristics of participants excluded due to a missing measure of baseline serum creatinine.

Supplemental Table 4. Demographic and health characteristics associated with risk of AKI in unadjusted and fully adjusted models and including the Charlson comorbidity index.

Supplemental Table 5. Demographic and health characteristics associated with the composite outcome of AKI stage 3, AKI requiring KRT, or death and the composite outcome of AKI requiring KRT or death.

Supplemental Table 6. Outcomes in the overall cohort of hospitalized patients with COVID-19 and by AKI stage among those who were discharged or had died.

Supplemental Table 7. Association of AKI status with mortality overall and in consideration of potential effect modification: (A) no interactions and with interaction of AKI with Black race, diabetes, and hypertension; (B) interactions of AKI with age, ADI, BMI category, and eGFR category.

Supplemental Table 8. Association of AKI severity with mortality.

Supplemental Table 9. Rates of AKI in hospitalized participants with COVID-19 and AKI stage within those who had an AKI, by calendar month.

References


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