Association of AKI-D with Urinary Findings and Baseline eGFR in Hospitalized COVID-19 Patients

Dipal M. Patel,1 Manali Phadke,2 Feng Dai,2 Michael Simonov,3 Neera K. Dahl,1 and Ravi Kodali1

Abstract

Background AKI is common in patients hospitalized with coronavirus disease 2019 (COVID-19). Risk factors for AKI requiring dialysis (AKI-D) are not fully understood. We aimed to identify risk factors associated with AKI-D and AKI not requiring dialysis (AKI-ND).

Methods We reviewed electronic health records of 3186 patients aged ≥18 years old who were hospitalized with COVID-19 across six hospitals. Patient characteristics, urinalysis findings, and inflammatory markers were analyzed for association with in-hospital AKI status (AKI-D, AKI-ND, or no AKI), and we subsequently evaluated mortality.

Results After adjustment for multiple covariates, higher baseline eGFR was associated with 30% lower odds of AKI-D and 11% lower odds of AKI-ND (for AKI-D, OR, 0.70; 95% CI, 0.64 to 0.77; for AKI-ND, OR, 0.89; 95% CI, 0.85 to 0.92). Patients with obesity and those who were Latino had increased odds of AKI-D, whereas patients with congestive heart failure or diabetes with complications had increased odds of AKI-ND. Females had lower odds of in-hospital AKI (for AKI-D, OR, 0.28; 95% CI, 0.17 to 0.46; for AKI-ND, OR, 0.83; 95% CI, 0.70 to 0.99). After adjustment for covariates and baseline eGFR, 1–4+ protein on initial urinalysis was associated with a nine-fold increase in odds of AKI-D (OR, 9.00; 95% CI, 2.16 to 37.38) and more than two-fold higher odds of AKI-ND (OR, 2.28; 95% CI, 1.66 to 3.13). Findings of 1–3+ blood and trace glucose on initial urinalysis were also associated with increased odds of both AKI-D and AKI-ND. AKI-D and AKI-ND were associated with in-hospital death (for AKI-D, OR, 2.64; 95% CI, 1.13 to 6.17; for AKI-ND, OR, 2.44; 95% CI, 1.77 to 3.35).

Conclusions Active urine sediments, even after adjustment for baseline kidney function, and reduced baseline eGFR are significantly associated with increased odds of AKI-D and AKI-ND. In-hospital AKI was associated with in-hospital death. These findings may help prognosticate patients hospitalized with COVID-19.

Key Points

- We evaluated risk factors for AKI requiring dialysis (AKI-D) in a cohort of 3186 patients hospitalized with coronavirus disease 2019.
- Patients who were Latino, men, and those with lower eGFR or obesity experienced more AKI-D. Patients with AKI-D had increased odds of mortality.
- After adjustment for covariates, including baseline kidney function, proteinuria and hematuria were associated with increased odds of AKI-D.

Introduction

AKI is commonly seen in coronavirus disease 2019 (COVID-19) and is associated with poor outcomes. Populations at risk for AKI in the setting of COVID-19 include those with CKD, diabetes, high body mass index (BMI), cardiovascular disease, and hypertension (HTN) (1). In one meta-analysis, AKI incidence ranged from 5% to 69% in patients hospitalized with COVID-19, with average incidences of 29% in patients hospitalized in the United States and Europe, and 6% in patients hospitalized in China (2). Pooled incidence of renal replacement therapy (RRT) was 8% in patients hospitalized in the United States and Europe. AKI in COVID-19 has consistently been associated with mortality (3–9),
with a risk ratio of 4.6 (95% CI, 3.3 to 6.5) on meta-analysis (2). Additional data on risk factors for development of AKI in the setting of COVID-19, and risk factors associated with progression to AKI requiring dialysis (AKI-D), may allow for better triage and prognostication of patients hospitalized with COVID-19. The patient population at risk for AKI-D is particularly important to identify, because mortality rates are >60% for patients hospitalized with COVID-19 in intensive care requiring RRT (10).

In this retrospective cohort analysis, we describe risk factors for the development of AKI-D in 3186 patients hospitalized with COVID-19 across six medical centers in the Northeastern United States. Our objectives were to identify patient characteristics, urinalysis (UA) findings, and inflammatory markers associated with risk of developing AKI-D and AKI not requiring dialysis (AKI-ND). We also evaluated the association of these clinical factors with in-hospital death. On the basis of our clinical experiences, we hypothesized that kidney tubular damage (resulting in proteinuria and hematuria), in addition to systemic inflammation (resulting in elevated inflammatory markers), would be associated with increased risk of AKI-D and mortality.

Methods

Study Population

The study was conducted across the Yale New Haven Health System, which includes five major hospitals (Yale New Haven Hospital, New Haven, CT; Bridgeport Hospital, Bridgeport, CT; Greenwich Hospital, Greenwich, CT; Lawrence Memorial Hospital, New London, CT; Westerly Hospital, Westerly, RI) and serves a large and diverse population of patients in the Northeastern United States. Deidentified patient data were obtained from electronic health records from patients hospitalized in this network between March 1 and September 17, 2020. The study was approved by the Yale Institutional Review Board (2000028702).

Patients were included if aged ≥18 years and hospitalized within the Yale New Haven Health System. All patients had a positive PCR test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 14 days before hospitalization or during the hospitalization, or were flagged as positive for SARS-CoV-2 in their electronic health records. The database included only inpatient encounters in which the patient’s first positive COVID-19 test was performed. “Only emergency department visits” were excluded, because patients needed to be hospitalized, either under observation status or under inpatient status. Patients were excluded if they did not have inpatient creatinine (Cr) measurements or if they had preexisting end stage kidney disease (ESKD), as per the coding of the International Classification of Diseases, Tenth Revision (ICD-10).

Data Collection

We collected information on demographics, comorbidities, procedures, medications, laboratory data, UA findings, and hospitalization metrics. All data were extracted from Clarity, the relational database used for data extraction and analysis for the Epic electronic health record. Preexisting conditions were identified using ICD-10 codes, as per Elixhauser ICD-based coding (11).

The primary definition for AKI was a 50% rise in serum Cr over the lowest Cr in the preceding 7 days, or a 0.3 mg/dl increase over the lowest value in the preceding 48 hours, corresponding to Kidney Disease Improving Global Outcomes (KDIGO) stage 1 AKI or higher. Our AKI definitions did not use urine output given a high degree of missingness in this variable. Dialysis was measured by utilization of dialysis-specific medications during the hospitalization; this definition was validated by manual inspection of a random sampling of patient medical records and was seen to have >95% sensitivity and specificity.

Historical baseline Cr and eGFR values were defined as a median of all Cr or eGFR values from 7 to 365 days preceding hospitalization. For patients with no baseline information available, baseline GFR was assumed to be 75 ml/min per 1.73 m², and baseline Cr was derived using the Chronic Kidney Disease Epidemiology Collaboration equation (12).

For UA data, urine protein and urine glucose were condensed into the following categories: 1–4+, trace, and absent. Urine blood was condensed into 1–3+, trace, and absent. Values for urine renal tubular epithelial (RTE) cells were combined into present or absent.

Definitions of Outcomes

The primary outcome was in-hospital AKI status (no AKI, AKI-ND, or AKI-D). The AKI-D group was defined as those who had AKI and continuous RRT (CRRT) or hemodialysis while hospitalized. All others who had AKI, but were not AKI-D, formed the AKI-ND group. Those who did not meet criteria for AKI formed the no AKI group. The secondary outcome was in-hospital death, defined as patients who were discharged from their hospitalization as deceased.

Statistical Analyses

Continuous variables are presented by AKI status as mean ±SD if normally distributed, or median (interquartile range [IQR]) if not normally distributed. Differences among groups were compared using ANOVA or Kruskal-Wallis tests. Categoric variables were presented as n (%) and compared using chi-squared or Fisher exact tests.

Multinomial logistic regression analysis was used to test the association of patient characteristics, urinary findings, and inflammatory markers with the primary outcome (AKI-D, AKI-ND, or no AKI). The first model, “model 1,” considered the following independent variables of demographics and comorbidities: sex, age, race, Latino, obesity, HTN without complication, HTN with complication, diabetes without complication, diabetes with complication, malignancy, congestive heart failure (CHF), and historical baseline eGFR. Subsequently, individual urinary findings and inflammatory markers were added to model 1 to test their respective association with the primary outcome. IL values (IL-2R, IL-6, and IL-10) were log transformed for analysis.

Multivariable logistic regression was used to assess the association of all independent variables in model 1 plus AKI status during hospitalization with in-hospital death (“model 2”). Last, another multivariable regression model was fit by adding maximum serum Cr, first UA protein, first UA glucose, first UA blood, maximum fibrinogen, maximum ferritin, maximum D-dimer, and maximum lactate in the


independent variable list (“model 3”). Logistic regression models are outlined in Supplemental Table 1 for reference.

To avoid multicollinearity in the regression analysis, if there were strong and significant correlations among different continuous factors ($r > 0.75$), only the factor with the least amount of missing data was entered in the regression models. Potential important covariates that had a large amount of missing data, such as ILs and a few other immune parameters, were also not included in multivariate models, as indicated.

All analysis was done using SAS version 9.4 (SAS Institute Inc., Cary, NC). No corrections for multiple testing were included. A two-sided $P$ value of $<0.05$ was considered statistically significant. The odds ratio (OR) and 95% CI of each independent variable in the models were reported as a measure of effect size. A 95% CI not containing the null value of one indicates statistical significance of the OR estimate. For AKI-D and AKI-ND that were not directly compared due to the choice of reference level (i.e., no AKI) in the logistic regression models, an indirect comparison was used by comparing the 95% CI range for the OR estimate of AKI-D versus no AKI to that of AKI-ND versus no AKI. CIs that were nonoverlapping indicated the existence of a statistically significant difference between AKI-D versus AKI-ND.

*Prior* sample size calculation and power analysis for this retrospective study were not performed, because we planned to include all patients aged $\geq$18 years who were hospitalized with COVID-19 between March 1, 2020 and September 17, 2020 in our health care system.

**Results**

**Patient Characteristics**

Of 3426 patients meeting inclusion criteria, 65 were excluded for lack of data on kidney function and 175 were excluded for preexisting ESKD, leaving a cohort of 3186 patients included in analysis (Figure 1). Six of the patients included in the analysis had kidney transplants. A total of 889 patients (27%) developed AKI, and 95 patients (3% of all patients and 11% of patients with AKI) developed AKI-D. A total of 45 patients required CRRT (1% of all patients, 5% of patients with AKI, and 47% of patients with AKI-D).

Patient characteristics are presented in Table 1. Of these patients, 48% were White, 25% were Black, and 27% were Latino. Males represented 76% of the AKI-D population. Historical baseline eGFR values were lower and obesity was more common in the AKI-D population compared with patients with AKI-ND or those without AKI, whereas prevalence of CHF, diabetes, HTN, and malignancy were similar in AKI-D and AKI-ND groups. The median serum Cr on admission was 1.5 (IQR, 1.0–2.7) for patients with AKI-D, compared with 1.2 (IQR, 0.8–1.8) for patients with AKI-ND and 0.9 (IQR, 0.7–1.2) for patients without AKI.

By univariate analysis, patients with higher BMI, obesity, CHF, diabetes, HTN, or higher serum Cr on admission had greater odds of developing AKI-D compared with patients with no AKI, whereas odds were lower for those with higher baseline eGFR and for females (Supplemental Table 2). In multinomial regression analysis (model 1), odds of AKI-D were found to be significantly elevated in Latino patients and those with obesity (Latino, OR, 2.54; 95% CI, 1.28 to 5.05; obesity, OR, 2.28; 95% CI, 1.42 to 3.67). Females and those with higher baseline eGFR had lower odds of AKI-D on multivariate analysis compared with females with AKI-D, OR, 0.28; 95% CI, 0.17 to 0.46; for females with AKI-ND, OR, 0.83; 95% CI, 0.70 to 0.99; baseline eGFR for AKI-D, OR, 0.70; 95% CI, 0.64 to 0.77; baseline eGFR for AKI-ND, OR, 0.89; 95% CI, 0.85 to 0.92) (Figure 2, Supplemental Table 2). Odds of AKI-ND were higher for patients who were older (OR, 1.01; 95% CI, 1.00 to 1.02), Black (OR, 1.29; 95% CI, 1.03 to 1.60), and for those with CHF (OR, 1.32; 95% CI, 1.03 to 1.70) or diabetes with complication (OR, 1.41; 95% CI, 1.09 to 1.83).

**UA Findings**

We evaluated findings obtained from the first UA of each patient’s hospitalization (Table 2). RTE cells were present in 89% of first UAs, and 86% of all patients had some degree of proteinuria. Although there was no significant difference in the presence of RTE cells between patient groups, patients with AKI-D more commonly had 1+ protein, 1+ blood, and trace glucose on first UA compared with patients with AKI-ND or those without AKI. A finding of 3+ protein was seen in 9% of all patients (7% of patients with no AKI, 14% of patients with AKI-ND, and 22% of patients with AKI-D).

Maximum urine albumin-Cr ratios and urine protein-Cr ratios (UPCRs) were higher in patients with AKI-D compared with other groups, respectively averaging 236.0 (IQR, 75.6–629.7) mg/g and 1.3 (IQR, 0.6–3.6) g/g for patients with AKI-D. UPCR values were $>3.5$ g/g, indicating nephrotic-range proteinuria, in 8% of patients with measured UPCR values (5% of patients with no AKI, 9% of patients with AKI-ND, and 26% of patients with AKI-D).

After adjusting for demographics, comorbidities, and baseline eGFR (model 1), we found increased odds of AKI-D in those presenting with 1+ protein, trace glucose, or 1+ blood on first UA (1+ protein, OR, 9.00; 95% CI, 2.16 to 37.38; trace glucose, OR, 3.96; 95% CI, 1.64 to 9.56; 1+ blood, OR, 2.96; 95% CI, 1.78 to 4.93) (Figure 3,
Supplemental Table 3). Odds of AKI-ND were higher in patients presenting with 1–4+ protein (OR, 2.28; 95% CI, 1.66 to 3.13), trace glucose (OR, 2.23; 95% CI, 1.34 to 3.73), 1–4+ glucose (OR, 1.65; 95% CI, 1.23 to 2.22), or 1–3+ blood (OR, 1.52; 95% CI, 1.23 to 1.87) on initial UA. Higher maximum urine albumin-Cr ratios and UPCRs were also associated with increased odds of both AKI-D and AKI-ND.

Figure 2. Odds of AKI-D were higher for Latinos and patients with obesity, whereas females and patients with higher baseline eGFR had lower odds of AKI-D. Odds ratios for the development of AKI-ND or AKI-D on multinomial analysis (model 1), using patients with no AKI as reference, are presented. Asterisks mark statistical significance (P-values are provided in Supplemental Table 2). CHF, congestive heart failure; HTN, hypertension; OR, odds ratio.
Inflammatory Markers

Maximum serum values of inflammatory markers (IL-2R, IL-6, IL-10, C-reactive protein, erythrocyte sedimentation rate, lactate, ferritin, fibrinogen, D-dimer, and lactate dehydrogenase) are shown in Supplemental Figure 1. Inflammatory markers were generally higher in patients with AKI-D compared with patients with AKI-ND and those without AKI. Both univariate and multivariate analysis showed that elevated IL-2R, IL-6, IL-10, fibrinogen, ferritin, D-dimer, lactate, C-reactive protein, and lactate dehydrogenase were associated with increased odds for both AKI-ND and AKI-D (Table 3, Supplemental Table 4).

Table 2. Urinalysis findings

| In-Hospital AKI Status | All  | No AKI | AKI-ND | AKI-D | P Valuea |
|------------------------|------|--------|--------|-------|----------|
| First UA RTE cells (n=807), n (%) |      |        |        |       |          |
| Absent                 | 92 (11) | 38 (9)  | 49 (15)  | 5 (7) | 0.09     |
| Present                | 715 (89) | 374 (91)  | 277 (85)  | 64 (93) | <0.001 |
| First UA protein (n=2192), n (%) |      |        |        |       |          |
| Absent                 | 302 (14) | 0242 (17)  | 0058 (8)  | 0002 (2) | <0.001 |
| Trace                  | 420 (19) | 0318 (23)  | 0097 (14)  | 0005 (5) |          |
| 1-4+                   | 1470 (67) | 0847 (60)  | 0538 (78)  | 0085 (92) |          |
| First UA glucose (n=2192), n (%) |      |        |        |       |          |
| Absent                 | 1820 (83) | 1216 (86)  | 0536 (77)  | 0668 (74) | <0.001 |
| Trace                  | 75 (3) | 0033 (2)  | 0034 (5)  | 0008 (9) |          |
| 1-4+                   | 297 (14) | 0158 (11)  | 0123 (18)  | 0016 (17) |          |
| First UA blood (n=2192), n (%) |      |        |        |       |          |
| Absent                 | 1099 (50) | 0779 (55)  | 0295 (43)  | 0025 (27) | <0.001 |
| Trace                  | 275 (13) | 0171 (12)  | 0096 (14)  | 0008 (9) |          |
| 1-3+                   | 818 (37) | 0457 (33)  | 0302 (44)  | 0059 (64) |          |
| Maximum urine ACR (mg/g), median (IQR) | 78.9 (32.3–324.0) | 65.4 (26.7–176.9)  | 145.5 (41.8–548.2)  | 236.0 (75.6–629.7) | <0.001 |
| Maximum urine PCR (g/g), median (IQR) | 0.4 (0.2–1.1) | 0.3 (0.2–0.7)  | 0.6 (0.3–1.3)  | 1.3 (0.6–3.6) | <0.001 |

Findings from first urinalyses and maximum proteinuria and albuminuria from hospitalization are shown. AKI-ND, AKI not requiring dialysis; AKI-D, AKI requiring dialysis; UA, urinalysis; RTE, renal tubular epithelial; ACR, albumin-creatinine ratio; IQR, interquartile range; PCR, protein-creatinine ratio.

aP values assess differences among groups.

Figure 3. | Odds of AKI-D were higher for those with 1-4+ urine protein, trace urine glucose, 1-3+ urine blood, or higher urine albumin/Cr or protein/Cr ratios. Odds ratios for the development of AKI-ND or AKI-D on multinomial analysis, using patients with no AKI as reference, are presented. Separate multinomial regression models were run for each factor, with each including patient characteristics listed in model 1. Asterisks mark statistical significance (P values are provided in Supplemental Table 3). Cr, creatinine; RTEs, renal tubular epithelial cells.
Hospitalization Characteristics

Characteristics of hospitalizations are shown in Supplemental Table 5. Patients in the AKI-D group had an average maximum serum Cr of 6.3 (IQR, 4.7–7.9) compared with 1.7 (IQR, 1.2–2.6) for those with AKI-ND and 1.0 (IQR, 0.8–1.2) for patients without AKI. Hospital length of stay was longer for patients with AKI-D and AKI-ND, with median lengths of stay of 26 (IQR, 14–37) days for patients with AKI-D, 15 (IQR, 9–24) days for patients with AKI-ND, and 6 (IQR, 3–11) days for patients without AKI. Of the 95 patients with AKI-D, 73 (77%) required intensive care unit care, with a median intensive care unit stay of 13 (IQR, 7–24) days.

Patients with AKI-ND and AKI-D demonstrated more acidosis, hypercarbia, and hypoxemia (Supplemental Table 5). Select medications administered during hospitalizations are also shown in Supplemental Table 5. Patients with AKI-D more commonly received vasopressors, steroids, and specialized COVID-19 therapies.

Mortality

Data on in-hospital death were captured for 1814 patients (91 with AKI-D, 633 with AKI-ND, and 1090 with no AKI). Of this patient subset, 16% died while hospitalized: 52 of the 91 patients (57%) with AKI-D, 234 of the 633 patients (37%) with AKI-ND, and 212 of the 1090 patients (19%) without AKI.

Our multivariate logistic regression model (model 2) showed that AKI-D was associated with >18-fold higher odds of in-hospital death (OR, 18.24; 95% CI, 11.06 to 30.08), whereas AKI-ND was associated with more than three-fold greater odds of in-hospital death (OR, 3.23; 95% CI, 2.57 to 4.07) compared with patients without AKI (Supplemental Table 6). Patients of an older age also had higher odds of in-hospital death (OR, 1.07; 95% CI, 1.06 to 1.08), whereas females and those with higher baseline eGFR had reduced odds of in-hospital death (females, OR, 0.74; 95% CI, 0.59 to 0.93; baseline eGFR, OR, 0.95; 95% CI, 0.90 to 0.99).

### Table 3. Association of inflammatory markers with AKI status

| Marker                        | AKI-ND versus No AKI, OR (95% CI) | P Value | AKI-D versus No AKI, OR (95% CI) | P Value |
|-------------------------------|-----------------------------------|---------|----------------------------------|---------|
| Maximum IL-6 (n=1277)         | 1.36 (1.26 to 1.47)               | <0.001  | 1.62 (1.37 to 1.91)              | <0.001  |
| Maximum IL-2R (n=1295)        | 1.39 (1.21 to 1.60)               | <0.001  | 2.63 (1.89 to 3.65)              | <0.001  |
| Maximum IL-10 (n=1282)        | 1.47 (1.27 to 1.71)               | <0.001  | 2.33 (1.75 to 3.11)              | <0.001  |
| Maximum fibrinogen (n=2890)   | 1.22 (1.16 to 1.30)               | <0.001  | 1.46 (1.26 to 1.71)              | <0.001  |
| Maximum ferritin (n=2946)     | 1.02 (1.02 to 1.03)               | <0.001  | 1.03 (1.02 to 1.03)              | <0.001  |
| Maximum D-dimer (n=3010)      | 1.06 (1.05 to 1.07)               | <0.001  | 1.14 (1.12 to 1.16)              | <0.001  |
| Maximum lactate (n=2226)      | 1.27 (1.20 to 1.34)               | <0.001  | 1.46 (1.36 to 1.57)              | <0.001  |
| Maximum CRP (n=1426)          | 1.08 (1.06 to 1.09)               | <0.001  | 1.17 (1.13 to 1.22)              | <0.001  |
| Maximum LDH (n=1456)          | 1.46 (1.37 to 1.56)               | <0.001  | 1.51 (1.41 to 1.62)              | <0.001  |

A separate multinomial logistic regression analysis was performed to test the association of each inflammatory marker with AKI status, adjusting for patient characteristics listed in model 1 (Supplemental Table 1). Log-transformed values of IL-6, IL-2R, and IL-10 were analyzed. For fibrinogen, ferritin, and LDH, a unit change of 100 was assumed in calculating OR. AKI-ND, AKI not requiring dialysis; AKI-D, AKI requiring dialysis; OR, odds ratio; CRP, C-reactive protein; LDH, lactate dehydrogenase.

### Table 4. Association of urinalysis findings, maximum serum Cr, and inflammatory markers with in-hospital death

| Marker                        | OR (95% CI) for In-Hospital Death | P Value |
|-------------------------------|----------------------------------|---------|
| First UA protein (versus absent) |                                  |         |
| Trace                         | 0.96 (0.56 to 1.64)              | 0.88    |
| 1–4+                          | 1.92 (1.23 to 2.99)              | 0.004   |
| First UA glucose (versus absent) |                                  |         |
| Trace                         | 0.67 (0.33 to 1.36)              | 0.26    |
| 1–4+                          | 1.45 (0.99 to 2.14)              | 0.06    |
| First UA blood (versus absent) |                                  |         |
| Trace                         | 1.14 (0.78 to 1.66)              | 0.51    |
| 1–3+                          | 1.52 (1.17 to 1.98)              | 0.002   |
| Maximum serum Cr              | 1.32 (1.20 to 1.45)              | <0.001  |
| Maximum IL-6                  | 1.10 (0.99 to 1.22)              | 0.06    |
| Maximum IL-2R                 | 0.92 (0.78 to 1.10)              | 0.36    |
| Maximum IL-10                 | 1.49 (1.23 to 1.80)              | <0.001  |
| Maximum fibrinogen            | 1.02 (0.95 to 1.10)              | 0.60    |
| Maximum ferritin              | 1.02 (1.01 to 1.02)              | <0.001  |
| Maximum D-dimer               | 1.06 (1.04 to 1.07)              | <0.001  |
| Maximum lactate               | 1.36 (1.28 to 1.45)              | <0.001  |

A separate multivariable logistic regression analysis was performed to test the association of each listed factor with in-hospital death, after adjusting for the covariates listed in model 2 (Supplemental Table 1). Fibrinogen and ferritin were analyzed using a unit change of 100. Log-transformed values of IL-6, IL-2R, and IL-10 were analyzed. Cr, creatinine; OR, odds ratio; UA, urinalysis.
In a separate logistic model after adjustment for the same list of independent variables in model 2, the presence of 1–4+ protein or 1–3+ blood on initial UA, in addition to elevated maximum serum Cr during hospitalization and maximum IL-10, ferritin, D-dimer, or lactate values, were associated with higher odds of in-hospital death (1–4+ UA protein, OR, 1.92; 95% CI, 1.23 to 2.99; 1–3+ UA blood, OR, 1.52; 95% CI, 1.17 to 1.98; maximum serum Cr, OR, 1.32; 95% CI, 1.20 to 1.45; maximum IL-10, OR, 1.49; 95% CI, 1.23 to 1.80; maximum ferritin, OR, 1.02; 95% CI, 1.01 to 1.02; maximum D-dimer, OR, 1.06; 95% CI, 1.04 to 1.07; maximum lactate, OR, 1.36; 95% CI, 1.28 to 1.45; Table 4).

Finally, in our most nonparsimonious regression model (model 3), increased odds of in-hospital death were seen in patients with AKI-D (OR, 2.64; 95% CI, 1.13 to 6.17), AKI-ND (OR, 2.44; 95% CI, 1.77 to 3.35), CHF (OR, 1.60; 95% CI, 1.08 to 2.38), older age (OR, 1.08; 95% CI, 1.06 to 1.10), higher maximum serum Cr (OR, 1.14; 95% CI, 1.02 to 1.28), or elevated inflammatory markers (maximum ferritin, OR, 1.01; 95% CI, 1.00 to 1.01; maximum D-dimer, OR, 1.04; 95% CI, 1.03 to 1.05; maximum lactate, OR, 1.23; 95% CI, 1.15 to 1.32) (Figure 4, Supplemental Table 7). Females and Black patients were at lower odds of in-hospital death (females, OR, 0.73; 95% CI, 0.53 to 1.00; Black race, OR, 0.59; 95% CI, 0.40 to 0.87). Historical baseline eGFR, after adjustments made in this model, was not associated with odds of in-hospital mortality.

### Discussion

In this study, we investigated patient characteristics and clinical factors associated with AKI-ND, AKI-D, and in-hospital death in patients hospitalized with COVID-19. Our study reveals several key findings that may be applicable to similarly diverse patient populations.

We found that patients with higher baseline eGFRs had a significant reduction in odds of AKI-D and AKI-ND. This finding supports an association between CKD and in-hospital AKI in the setting of COVID-19 (1). Reduction in odds of in-hospital AKI was also found for female patients.

Proteinuria and hematuria have been reported to be highly prevalent in patients with COVID-19. In one cohort of patients with COVID-19, 64% presented with hematuria and 75% with proteinuria on urine dipstick (5). Notably, the incidence of proteinuria and hematuria may actually
exceed that of AKI, raising the possibility that urinary abnormalities could serve as an earlier, or more sensitive, marker of disease (13). Others have demonstrated an association of proteinuria and hematuria with mortality in the setting of disease (13). Others have demonstrated an association of proteinuria with the need for dialysis in 84 patients with formal UPCRs (23). We demonstrate an association of proteinuria and hematuria on initial UA with higher odds for AKI-D and AKI-ND, with nine-fold higher odds of AKI-D in patients with 1–4+ protein on initial UA. Importantly, this association stands despite adjustment for historical baseline eGFR. Trace urine glucose, which may represent tubular dysfunction, was also associated with increased odds of AKI-D. UA screening is likely attainable for most patients hospitalized with COVID-19 and should be used for prognostication, even when unable to measure formal UPCRs in resource-limited settings.

Although mechanistic evaluation with kidney biopsy specimens was not reported in our study, we feel that our data implicate a tubulointerstitial pattern of damage caused by SARS-CoV-2, resulting in nonalbumin proteinuria, trace glucosuria, and hematuria (17,24,25). Of the patients with AKI-D, 26% had nephrotic-range proteinuria in our study, supporting what others have shown to be a range of kidney injury pathologies in COVID-19, including both tubular injury and glomerular processes (26–35).

SARS-CoV-2 is proposed to trigger a systemic inflammatory response (1), and we, therefore, evaluated the association of inflammatory markers with outcomes in patients hospitalized with COVID-19. Some studies have reported elevated IL-6 levels as being associated with AKI (35) and death (36,37), although others have reported that the association is not significant after adjustment for covariates (38) and on meta-analysis (39). In our study, elevated inflammatory marker values were associated with AKI-D and AKI-ND. Elevation of inflammatory markers is associated with poor outcomes, but measurement of these factors may not be as available in resource-limited settings, and, furthermore, may not be a risk factor immediately apparent at the time of hospitalization.

AKI-D and AKI-ND were associated with higher odds of in-hospital death, similar to data from additional patient cohorts (3–9). Our data support evidence that males and the elderly are at increased risk of death in the setting of COVID-19 (40–43). In our patient cohort, Latino patients had higher odds of AKI-D, but not in-hospital death, whereas Black patients had lower odds of in-hospital death. Black patients have been shown to be at higher risk of mortality in the setting of COVID-19 infection, even after adjustment for covariates (40,43), although others have also shown decreased mortality (41,42). Further data are needed to understand variations in patient populations, including socioeconomic factors, that may explain these disparate findings.

Strengths and Limitations

A major strength of our study was the inclusion of data from a large hospital network, offering information on a diverse patient population. Our study is one of a few that examine associations of urinary findings and inflammatory markers with outcomes of AKI-D and mortality. We separated associations of trace versus significant proteinuria, hematuria, or glucosuria with studied outcomes, and provided data on albuminuria and total proteinuria for patient groups.

There were several limitations to our study. Prehospitalization baseline proteinuria was not captured, although baseline kidney function was included in analysis. Given lack of data on urine output for all patients, we did not categorize patients per KDIGO stages of AKI, and instead categorized patients as AKI with or without the need for dialysis. Notably, patients who may have had indications for dialysis, but did not start dialysis due to goals of care or other issues (such as resource allocation), were not included in the AKI-D group. We did not track progression of AKI or posthospitalization outcomes of residual kidney disease and dialysis dependency, although this information has been published elsewhere (44). Outcomes for the small number of kidney transplant patients were not separately analyzed. We did not specifically evaluate risk factors associated with need for CRRT. We did not account for the influence of dialysis and/or medications in changes to inflammatory marker values, and did not evaluate the association of administered medications with outcomes. In-hospital death was evaluated without time-to-event analysis.

In a diverse population of 3186 patients hospitalized with COVID-19, 27% developed AKI, of which 11% required initiation of dialysis. Patients with 1–4+ proteinuria on initial UA had the highest odds for development of AKI-D, and patients with AKI-D had the highest odds for in-hospital death. The association of inflammatory markers with outcomes was moderate. We advocate for standardized assessment of UA in addition to traditional risk factors, including preexisting kidney disease, as tools to prognosticate patients admitted with COVID-19.

Disclosures

N.K. Dahl reports receiving research funding as a principal investigator for clinical trials sponsored by Allena, Kadmon, Reata, Regulus, and Sanofi; serving on the medical advisory board for ESRD Network, Region 1, and on the medical advisory board for the National Kidney Foundation New England Chapter; serving as a scientific advisor for, or member of, Natera and PKD Foundation; receiving honoraria from National Kidney Foundation and Otsuka Pharmaceutical; and having consultancy agreements with Otsuka Pharmaceuticals. All remaining authors have nothing to disclose.
Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.00161201/---DCSupplemental.

Supplemental Figure 1. Maximum inflammatory marker values.

Supplemental Table 1. Description of logistic regression models.

Supplemental Table 2. Association of patient characteristics with AKI status.

Supplemental Table 3. Association of urinary findings with AKI status.

Supplemental Table 4. Association of inflammatory markers with AKI status.

Supplemental Table 5. Hospitalization characteristics.

Supplemental Table 6. Association of patient characteristics with in-hospital death.

Supplemental Table 7. Association of patient characteristics, urinary findings, and inflammatory markers with in-hospital death.

References

1. Nadim MK, FORNI LG, Mehta RL, FORN Jr MJ, Liu KD, Osterman M, Rimmelze T, Zarkoob A, Bell S, Bhorac A, Cantaluppi V, Hoste E, Husain-Sayed F, Germain MJ, Goldstein SL, Gupta S, Journidis M, Kashani K, Keyner J, Legrand M, Lumintzguel N, Minahan S, Patunoo N, Peng Z, Perez-Fernandez XL, Pickek D, Prowle J, Reis T, Srisawat N, Tolwani A, Vijayan A, Villa G, Yang L, Ronco C, Kellum JA: COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 16: 747–764, 2020.

2. Fu EL, Janse BJ, de Jong Y, van der Endt VHW, Malders J, van der Willik EM, de Rooij enM, Dekkers OM, rotman JS, van Diepen MJ: Acute kidney injury and kidney replacement therapy in COVID-19: A systematic review and meta-analysis. Clin Kidney J 13: 550–563, 2020 https://doi.org/10.1093/ckj/sfia160

3. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, Alotaibi A, Silva RM, Saha S, Singh S, Tse KE, Tan WW, Yuan L, Adhikari N, Friesen DE, Senior RS, Balasubramaniam T, Chan AW, Böttiger EP, Glicksberg BS, Coca SG, Nadkarni GM, Mount Sinai COVID-19 Informatics Center (MSCIC): AKI in hospitalized patients with COVID-19. J Am Soc Nephrol 32: 151–160, 2020.

4. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu C: Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 97: 829–838, 2020 https://doi.org/10.1016/j.kint.2020.03.005

5. Hirschl JS, Ng IH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaeveri KD: Northwell COVID-19 Research Consortium; Northwell Nephrology Nephropathy COVID-19 Research Consortium: Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 98: 209–218, 2020 https://doi.org/10.1016/j.kint.2020.05.006

6. Lim MA, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R: Multiorgan failure with emphasis on acute kidney injury and severity of COVID-19: Systematic review and meta-analysis [published online ahead of print July 7, 2020]. Can J Kidney Health Dis 10.1177/2054358120938573

7. Robbins-Juarez SY, Qian L, Stevens JS, Husain SA, Radhakrishnan J, Mohan S: Outcomes for Patients With COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. Kidney Int Rep 5: 1149–1160, 2020 https://doi.org/10.1016/j.ekir.2020.06.013

8. Shao M, Li X, Liu F, Tian T, Luo J, Yang Y: Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: A systematic review and meta-analysis of 40 studies and 24,527 patients. Pharmacol Res 161: 105107, 2020 https://doi.org/10.1016/j.phrs.2020.105107

9. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, Zhou T, Yuan Y, Qi H, Su S, Liu H, Xia J, Xu Z, Yu Y, Li R, Ouyang Y, Wang R, Ren L, Hu Y, Xu D, Zhao X, Yuan S, Zhang D, Shang Y: Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: A multicenter retrospective study from Wuhan, China. Crit Care 24: 394, 2020 https://doi.org/10.1186/s13054-020-03098-9

10. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, Sutherland A, Puri S, Srivastava A, Leonberg-Yoo A, Shehata AM, Flythe JE, Rashidi A, Schench EI, Goyal N, Hedayati SS, Dy R, Bansal A, Athavale A, Nguyen HB, Vijayan A, Charytan DM, Schulze CE, Joo MJ, Friedman AN, Zhang J, Sosa MA, Judd E, Velez JCQ, Mallapurapalli M, Reddern EA, Bansal AD, Nejra JA, Liu KD, Renagdan AD, Christov M, Molnar MZ, Sharma S, Kamal O, Boateng JO, Short SAP, Admon AJ, Sze ME, Wang W, Parikh R, Leaf DE: STOP-COVID Investigators: AKI treated with renal replacement therapy in critically ill patients with COVID-19. J Am Soc Nephrol 32: 161–176, 2020 https://doi.org/10.1681/ASN.2020060897

11. Elshauser A, Steiner C, Harris DR, Coffey RM: Comorbidities measures for use with administrative data. MedCare 36: 8–27, 1998 https://doi.org/10.1016/S0025-5844(1998)100-0004-0

12. Yang X, Jin Y, Li R, Zhang Z, Sun R, Chen D: Prevalence and findings with AKI inflammatory marker values. Kidney Int 88: 563–568, 2020 https://doi.org/10.1016/j.kint.2020.05.006

13. Yang Y, Jin Y, Li R, Zhang Z, Sun R, Chen D: Prevalence and impact of acute renal impairment on COVID-19: A systematic review and meta-analysis. Crit Care 24: 356, 2020 https://doi.org/10.1186/s13054-020-03065-4

14. Bonetti G, Manelli F, Bettinardi A, Borrelli G, Fiordalisi G, Marino A, Menolfi A, Saggini S, Volpi R, Adaminii R, Lippi G: Urinalysis parameters for predicting severity in coronavirus disease 2019 (COVID-19). Clin Chem Lab Med 58: e163–e165, 2020 https://doi.org/10.1515/cclm-2020-0576

15. Chaudhri I, Moffitt R, Taub E, Annadi RR, Hoxi M, Bolotova O, Yoo J, Dhaliai S, Sahib H, Daccuel F, Hajagos J, Saltz M, Saltz J, Mallipattu SK, Koraishy FM: Association of proteinuria and hematuria with acute kidney injury and mortality in hospitalized patients with COVID-19. Kidney Blood Press Res 45: 1018–1032, 2020 https://doi.org/10.1007/s40619-020-02282-9

16. Hong D, Long I, Wang AY, Lei Y, Tang Y, Zhao JW, Song X, He Y, Wen E, Zheng L, Li G, Wang L: Kidney manifestations of mild, moderate and severe coronavirus disease 2019: A retrospective cohort study. Clin Kidney J 13: 340–346, 2020 https://doi.org/10.1093/ckj/ssta083

17. Huet J, Bourqueguene A, Lutteri E, Erpicum P, Grosch S, Resimont G, Wiesen P, Bowy C, Krzesinski JM, Thys M, Lambertz B, Missel B, Pottel H, Mariat C, Cavalier E, Burtey S, Jouret F, Delanaye P: Proteinuria in COVID-19: Prevalence, characterization and prognostic role. J Nephrol 34: 355–364, 2021 https://doi.org/10.1007/s40665-020-00931-w

18. Husain-Sayed F, Wilhelm J, Kassoumeh S, Birk HW, Herold S, Vardas I, Walnath HD, Kellum JA, Ronco C, Seeger W: Acute kidney injury and urinary biomarkers in hospitalized patients with coronavirus disease-2019. Nephrol Dial Transplant 35: 1271–1274, 2020 https://doi.org/10.1093/ndt/gja162

19. Liu R, Ma Q, Han Q, Han H, Su H, Liu F, Wu K, Wang W, Zhu C: The value of urine biochemical parameters in the prediction of the severity of coronavirus disease 2019. Clin Chim Acta 58: 1121–1124, 2020 https://doi.org/10.1016/j.cca.2020.02.020

20. Ouahmi J, Courjon J, Morand I, François J, Bruckert V, Lombard R, Esnault V, Seitz-Polski B, Demonchy E, Dellamonica J, Boyer-Suvaet S: Proteinuria as a biomarker for COVID-19 severity. Front Physiol 12: 611772, 2021 https://doi.org/10.3389/fphys.2021.611772
