Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Comparison of COVID-19 versus influenza on the incidence, features, and recovery from acute kidney injury in hospitalized United States Veterans

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Acute kidney injury is a common complication in patients hospitalized with SARSCoV-2 (COVID-19), with prior studies implicating multiple potential mechanisms of injury. Although COVID-19 is often compared to other respiratory viral illnesses, few formal comparisons of these viruses on kidney health exist. In this retrospective cohort study, we compared the incidence, features, and outcomes of acute kidney injury among Veterans hospitalized with COVID-19 or influenza and adjusted for baseline conditions using weighted comparisons. A total of 3402 hospitalizations for COVID-19 and 3680 hospitalizations for influenza admitted between October 1, 2019 and May 31, 2020 across 127 Veterans Administration hospitals nationally were studied using the electronic medical record. Acute kidney injury occurred more frequently among those with COVID-19 compared to those with influenza (40.9% versus 29.4%, weighted analysis) and was more severe. Patients with COVID-19 were more likely to require mechanical ventilation and vasopressors and experienced higher mortality. Proteinuria and hematuria were frequent in both groups but more common in COVID-19. Recovery of kidney function was less common in patients with COVID-19 and acute kidney injury but was similar among survivors. Thus, findings from this study confirm that acute kidney injury is more common and severe among patients hospitalized with COVID-19 compared to influenza, a finding that may be driven largely by illness severity. Hence, the combined impact of these two illnesses on kidney health may be significant and have important implications for resource allocation.

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KEYWORDS: acute kidney injury; COVID-19; hematuria; influenza; proteinuria

Acute kidney injury (AKI) is a well-recognized complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19]),[1–4] occurring in one-third of hospitalized patients and up to three-quarters of critically ill patients,[1,2,4] with associated in-hospital mortality rates of up to 50%.[1,4] The reasons underlying the high AKI incidence rates and associated poor outcomes are not well understood. High rates of hematuria and proteinuria have also been observed in COVID-19.

The extent to which these findings differ from other severe viral respiratory illnesses is unknown. Although informal comparisons to influenza have been made, few direct comparisons have been performed. Literature on AKI in influenza suggests some risk factors common to both illnesses, such as those related to illness severity (e.g., critical illness and mechanical ventilation).[5–8] Similarly, elevated inflammatory markers have been observed in both influenza and COVID-19 and are often associated with AKI,[5,8–12] whereas histopathologic data and clinical studies suggest ischemic injury as the predominant etiology of AKI in both illnesses.[13–19] Further understanding of the relative and combined burden of AKI in these 2 illnesses is critical. We hypothesized that patients with COVID-19 would have higher rates and severity of AKI than similar patients hospitalized with influenza. To test this hypothesis, we compared the incidence, risk factors, clinical features, and recovery from AKI in a retrospective study of veteran patients hospitalized with either COVID-19 or influenza.

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METHODS

Study setting and design

We conducted a national retrospective cohort study of veterans, aged ≥18 years, who were admitted with COVID-19 or influenza between October 1, 2019, and May 31, 2020. Data were obtained from the electronic health record utilized by the Veterans Affairs (VA) Health Administration, which is composed of the Veterans Health Information and Technology Architecture and Computerized Patient Record System. This study was approved by the Institutional Review Board and the Research and Development Committee of the Tennessee Valley Healthcare System VA. The requirement for informed consent was waived because of the infeasibility of obtaining informed consent for a large national cohort.

Data collection

Data from October 1, 2018, to September 24, 2020, were collected from the Observational Medical Outcomes Partnership version 5 common data model transformation of the National Corporate Data Warehouse, which aggregates data from all VA facilities, and the VA COVID-19 Shared Data Resource.[20–22] Complete hospitalization information was available for all patients. Baseline comorbidity data were obtained from available records up to the day of hospital admission. Inpatient conditions, vital signs, laboratory data, and exposures were obtained from records from admission through discharge. Kidney function and mortality outcomes were collected from VA laboratory data, administrative diagnosis and procedure codes, and VA vital status files. Diagnoses and procedures were defined using the *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Classification of Diseases, Tenth Revision* (*ICD-10*), and Current Procedural Terminology codes (Supplementary Table S1). Laboratory tests were identified by Logical Observation Identifiers Names and Codes. Medications were obtained from outpatient VA pharmacy fill records and inpatient barcoded medication administration and categorized using the Anatomical Therapeutic Chemical classification and RxNorm.

Cohort exclusion criteria

Within the predefined study time frame and across 127 VA hospitals nationally, we identified 8454 hospitalizations that included a diagnosis of COVID-19 or influenza. Eligibility criteria included either a premorbid outpatient serum creatinine value and at least 1 inpatient serum creatinine value or at least 2 serum creatinine values in the absence of a premorbid baseline value. We applied several exclusion criteria to provide the 2 clinically relevant cohorts, as illustrated in Figure 1. We excluded patients who underwent nephrectomy during the hospitalization and patients with a baseline estimated glomerular filtration rate (eGFR) <15 ml/min per 1.37 m^2, kidney transplantation, or end-stage renal disease before index hospitalization. In patients who had >1 qualifying hospitalization during the study period, we restricted to the first qualifying hospitalization. Patients with both a positive COVID-19 and influenza test during the study period were excluded.

Definitions

The primary exposures in this study were infection with COVID-19 or influenza. Two groups were defined: (i) patients with a positive COVID-19 test within 14 days before or during the hospitalization; and (ii) patients with a positive influenza A or influenza B test within 14 days before or during the hospitalization. Patients were diagnosed with COVID-19 or influenza by polymerase chain reaction–based or rapid antigen tests of nasopharyngeal, oropharyngeal, or respiratory specimens. The primary outcome in this study was AKI. AKI was defined using the peak in-hospital serum creatinine and staged using modified Kidney Disease: Improving Global Outcomes (KDIGO) creatinine-based criteria: stage 1, ≥0.3 mg/dl creatinine increase from baseline or creatinine 1.5 to 1.9 times baseline; stage 2, creatinine 2.0 to 2.9 times baseline; and stage 3, creatinine 3.0 times baseline or initiation of dialysis.[23] To more accurately compare AKI staging and recovery, we preferred to anchor our definition to a known baseline creatinine, which was available in 84% of patients with COVID-19 and 92% with influenza. Secondary outcomes included hematuria, proteinuria, kidney replacement therapy,

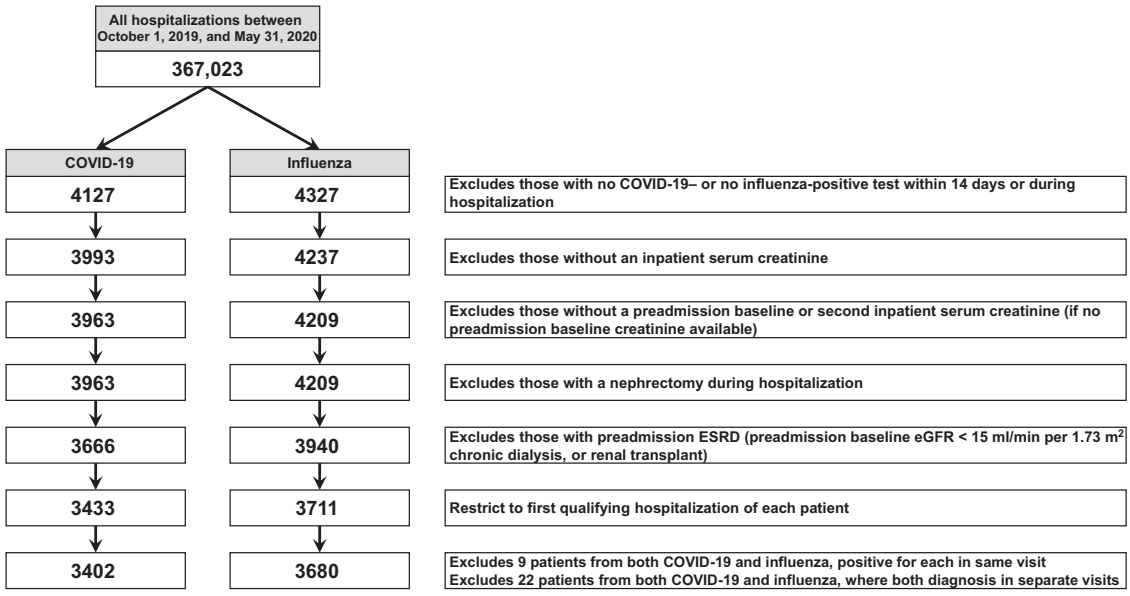

Figure 1 | Cohort selection flow diagram. Exclusion criteria applied to eligible hospitalizations to derive final study groups. COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease.

Table 1 | Baseline characteristics of unweighted cohorts

Demographics and comorbidities	Total (N = 7082)	No. nonmissing	COVID-19–positive (N = 3402)	No. nonmissing	Influenza-positive (N = 3680)	No. nonmissing	SMD
Age, yr, mean (SD)	67.3 (13.5)	7082	68.3 (13.9)	3402	66.5 (13.1)	3680	**0.137**
Female, n (%)	468 (7)	7082	203 (6)	3402	265 (7)	3680	0.050
Race, n (%)		7082		3402		3680	
Unknown	485 (7)		272 (8)		213 (6)		0.087
African American	2494 (35)		1583 (47)		911 (25)		**0.467**
Other	151 (2)		62 (2)		89 (2)		0.041
White	3952 (56)		1485 (44)		2467 (67)		**0.484**
Ethnicity, n (%)		7082		3402		3680	
Unknown	205 (3)		107 (3)		98 (3)		0.029
Hispanic/Latino	524 (7)		292 (9)		232 (6)		0.087
Not Hispanic/Latino	6353 (90)		3003 (88)		3350 (91)		0.091
Diabetes mellitus, n (%)	3581 (51)	7082	1790 (53)	3402	1791 (49)	3680	0.079
Hypertension, n (%)	5915 (84)	7082	2804 (82)	3402	3111 (85)	3680	0.057
Coronary artery disease, n (%)	3219 (45)	7082	1434 (42)	3402	1785 (49)	3680	**0.128**
Peripheral vascular disease, n (%)	2336 (33)	7082	1074 (32)	3402	1262 (34)	3680	0.058
Heart failure, n (%)	2220 (31)	7082	938 (28)	3402	1282 (35)	3680	**0.157**
Mild liver disease, n (%)	1525 (22)	7082	727 (21)	3402	798 (22)	3680	0.008
Moderate to severe liver disease, n (%)	194 (3)	7082	90 (3)	3402	104 (3)	3680	0.011
Chronic obstructive pulmonary disease, n (%)	3944 (56)	7082	1589 (47)	3402	2355 (64)	3680	**0.353**
Cancer (*ICD-9*), n (%)	1918 (27)	7082	834 (25)	3402	1084 (29)	3680	**0.111**
Cerebrovascular disease, n (%)	2076 (29)	7082	991 (29)	3402	1085 (29)	3680	0.008
Myocardial infarction, n (%)	1304 (18)	7082	529 (16)	3402	775 (21)	3680	**0.143**
Dementia, n (%)	1020 (14)	7082	649 (19)	3402	371 (10)	3680	**0.257**
Hemiplegia or paraplegia, n (%)	465 (7)	7082	230 (7)	3402	235 (6)	3680	0.015
HIV, n (%)	148 (2)	7082	64 (2)	3402	84 (2)	3680	0.028
Peptic ulcer disease, n (%)	585 (8)	7082	241 (7)	3402	344 (9)	3680	0.083
Rheumatic disease, n (%)	301 (4)	7082	127 (4)	3402	174 (5)	3680	0.049
Metastatic solid tumor, n (%)	376 (5)	7082	148 (4)	3402	228 (6)	3680	0.083
Baseline eGFR, ml/min per 1.73 m^2, mean (SD)	73.9 (22.5)	6271	73.3 (23.2)	2863	74.3 (22.0)	3408	0.045
Last preadmission BMI, kg/m^2, mean (SD)	30.2 (7.1)	5972	30.6 (7.0)	2735	29.9 (7.1)	3237	0.090
Last preadmission temperature, ° C, mean (SD)	98.0 (0.9)	6607	98.1 (0.9)	3076	98.0 (0.8)	3531	**0.181**
Last preadmission SBP, mm Hg, mean (SD)	131 (19)	6641	132 (19)	3093	131 (19)	3548	0.052
Last preadmission DBP, mm Hg, mean (SD)[a]	76 (11)	6640	76 (11)	3092	76 (11)	3548	0.045
Last preadmission pulse, bpm, mean (SD)	80 (15)	6640	80 (15)	3092	80 (15)	3548	0.011
Last preadmission O_2 saturation, %, mean (SD)	96.3 (2.6)	6451	96.6 (2.3)	2995	96.0 (2.8)	3456	**0.205**
Last preadmission protein dipstick, n (%)		7082		3402		3680	**0.235**
Not measured	2994 (42)		1641 (48)		1353 (37)		
Negative or trace	2838 (40)		1211 (36)		1627 (44)		
1+	663 (9)		285 (8)		378 (10)		
≥2+	587 (8)		265 (8)		322 (9)		
Last preadmission urine dipstick RBCs, n (%)		7082		3402		3680	**0.222**
Not measured	3068 (43)		1662 (49)		1406 (38)		
Negative or trace	3153 (45)		1340 (39)		1813 (49)		
1+	497 (7)		234 (7)		263 (7)		
≥2+	364 (5)		166 (5)		198 (5)		
Active ACE inhibitor user, n (%)[b]	1515 (21)	7082	625 (18)	3402	890 (24)	3680	**0.142**
Active ARB user, n (%)[b]	768 (11)	7082	334 (10)	3402	434 (12)	3680	0.064
Active CCB user, n (%)[b]	1538 (22)	7082	748 (22)	3402	790 (21)	3680	0.013
Active α-blocker user, n (%)[b]	221 (3)	7082	83 (2)	3402	138 (4)	3680	0.076
Active β-blocker user, n (%)[b]	1959 (28)	7082	709 (21)	3402	1250 (34)	3680	**0.298**
Active K-sparing diuretic user, n (%)[b]	312 (4)	7082	126 (4)	3402	186 (5)	3680	0.066
Active loop diuretic user, n (%)[b]	893 (13)	7082	296 (9)	3402	597 (16)	3680	**0.229**

(*Continued on following page*)

Table 1 | (Continued)

Demographics and comorbidities	Total (N = 7082)	No. nonmissing	COVID-19–positive (N = 3402)	No. nonmissing	Influenza-positive (N = 3680)	No. nonmissing	SMD
Active thiazide user, n (%)[b]	891 (13)	7082	450 (13)	3402	441 (12)	3680	0.037
Active peripheral vasodilator user, n (%)[b]	190 (3)	7082	93 (3)	3402	97 (3)	3680	0.006
Recent acyclovir fill, n (%)[c]	98 (1)	7082	26 (1)	3402	72 (2)	3680	**0.103**
Recent azithromycin fill, n (%)[c]	2098 (30)	7082	775 (23)	3402	1323 (36)	3680	**0.292**
Recent β-lactam fill, n (%)[c]	512 (7)	7082	212 (6)	3402	300 (8)	3680	0.074
Recent cephalosporin fill, n (%)[c]	344 (5)	7082	127 (4)	3402	217 (6)	3680	**0.101**
Recent hydroxychloroquine fill, n (%)[c]	37 (1)	7082	19 (1)	3402	18 (0)	3680	0.010
Recent fluoroquinolone fill, n (%)[c]	271 (4)	7082	85 (2)	3402	186 (5)	3680	**0.134**
Recent H2 blocker fill, n (%)[c]	436 (6)	7082	171 (5)	3402	265 (7)	3680	0.091
Recent NSAID fill, n (%)[c]	942 (13)	7082	406 (12)	3402	536 (15)	3680	0.078
Recent proton pump inhibitor fill, n (%)[c]	1706 (24)	7082	648 (19)	3402	1058 (29)	3680	**0.229**
Recent steroid fill, n (%)[c]	958 (14)	7082	247 (7)	3402	711 (19)	3680	**0.361**

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *ICD-9*, *International Classification of Diseases, Ninth Revision*; NSAID, nonsteroidal anti-inflammatory drug; RBC, red blood cell; SBP, systolic blood pressure; SMD, standardized mean difference.
[a]DBP indicator variable for missingness not included in the logistic regression model because of collinearity with the SBP indicator variable for missingness.
[b]Active user refers to pills on hand at admission.
[c]Recent fill refers to fill within last 104 days.
SMDs are the absolute difference in means or percentages divided by an evenly weighted pooled SD or difference between groups in number of SDs. Bolded values denote SMD values >0.1, indicating imbalance between the groups.

recovery from AKI, and death in hospital and at 90 days following peak serum creatinine. Recovery from AKI was defined by serum creatinine value within 20% of baseline serum creatinine, obtained within the following time frames: within 4, 30, and 90 days of peak serum creatinine.

Other definitions

Baseline serum creatinine to define AKI was the mean outpatient serum creatinine value 7 to 365 days before hospitalization.[24] Among those without a known preadmission baseline, we used the lowest serum creatinine during hospitalization. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[25] Hematuria and proteinuria were defined as 1+ or higher red blood cells or protein on urine dipstick, respectively. Acute dialysis was defined using procedure codes (Supplementary Table S1). Death was ascertained through VA Vital Status File, which aggregates date of death from several locations.[26]

Covariates

Baseline comorbidities were ascertained in the preadmission time frame up to but not including the day of admission (Supplementary Table S1). Preadmission medication exposures were ascertained from 104 days before admission up to the admission date. In-hospital exposures included vital signs, laboratory results, medications, and mechanical ventilation.

Statistical approach

The primary analysis compared AKI incidence during hospitalization, mortality during hospitalization and within 90 days of peak serum creatinine, and AKI recovery occurring within 90 days of peak serum creatinine between patients hospitalized with COVID-19 or influenza. To account for measured confounding, an inverse probability of treatment weighted cohort was created that balanced the distributions of >50 observed covariates (Tables 1 and 2). The weights were calculated using the matching weight formula that creates covariate distributions similar to a 1-to-1 propensity score matched cohort.[27] These weights are highly efficient, allowing the use all of the patients in the cohort while avoiding the potentially extreme weights of other methods. The propensity score used for the weighting was calculated via a logistic regression model predicting COVID-19 versus influenza. The model included 55 prehospitalization covariates, including major variables known to increase the risk for mortality, such as hypertension medications, history of congestive heart failure, proteinuria (dipstick), mean preadmission outpatient eGFR, and extensive comorbidities. To balance missingness patterns, missing values for preadmission body mass index (15.7%), preadmission temperature (6.7%), preadmission systolic blood pressure (6.2%), preadmission diastolic blood pressure (6.2%), preadmission pulse (6.2%), preadmission oxygen saturation (8.9%), and baseline eGFR (11.5%) were set to low leverage points (global means), and indicator variables for missingness were included in the propensity score model.[28] This approach for balancing missingness patterns is preferred for a propensity score model, as opposed to a covariate-adjusted model of the outcome, where multiple imputation may be preferred. Covariate balance in the inverse probability of treatment weighted cohort was assessed using standardized mean differences (Tables 1 and 2). The weighted cohorts for patients hospitalized with COVID-19 or influenza who were (i) diagnosed with AKI or (ii) diagnosed with AKI and survived 90 days after peak were created using the same method. All analyses were conducted using R software version 4.0.2 (R Foundation for Statistical Computing).[29] Confidence intervals and *P* values were calculated using the "survey" package in R to account for the inverse probability treatment weights. *P* values were calculated using χ^2 tests with a continuity correction for categorical variables and 2-sample *t* tests for continuous variables.

RESULTS

We identified 7082 patients admitted to 127 VA hospitals between October 1, 2019, and May 31, 2020, who met eligibility criteria. Of these patients, 3402 had a diagnosis of COVID-19 and 3680 had a diagnosis of influenza. The distribution of hospitalization dates is shown in Figure 2, with most influenza hospitalizations occurring between December

Table 2 | Baseline characteristics of weighted cohorts

Demographics and comorbidities	Total $W = 4480$	No. nonmissing	COVID-19–positive $W = 2247$	No. nonmissing	Influenza-positive $W = 2233$	No. nonmissing	SMD
Age, mean yr, (SD)	66.9 (13.7)	4480	66.9 (13.7)	2247	66.9 (13.7)	2233	0.002
Female, n (%)	289 (6)	4480	145 (6)	2247	144 (6)	2233	<0.001
Race, n (%)		4480		2247		2233	
Unknown	317 (7)		159 (7)		158 (7)		<0.001
African American	1601 (36)		804 (36)		798 (36)		0.001
Other	105 (2)		53 (2)		52 (2)		0.002
White	2456 (55)		1231 (55)		1226 (55)		0.002
Ethnicity, n (%)		4480		2247		2233	
Unknown	132 (3)		66 (3)		65 (3)		0.002
Hispanic/Latino	363 (8)		183 (8)		180 (8)		0.003
Not Hispanic/Latino	3985 (89)		1997 (89)		1988 (89)		0.004
Diabetes mellitus, n (%)	2299 (51)	4480	1151 (51)	2247	1148 (51)	2233	0.003
Hypertension, n (%)	3731 (83)	4480	1871 (83)	2247	1861 (83)	2233	0.002
Coronary artery disease, n (%)	2010 (45)	4480	1003 (45)	2247	1006 (45)	2233	0.008
Peripheral vascular disease, n (%)	1452 (32)	4480	726 (32)	2247	726 (33)	2233	0.004
Heart failure, n (%)	1383 (31)	4480	694 (31)	2247	689 (31)	2233	0.001
Mild liver disease, n (%)	984 (22)	4480	490 (22)	2247	494 (22)	2233	0.007
Moderate to severe liver disease, n (%)	122 (3)	4480	61 (3)	2247	61 (3)	2233	0.002
Chronic obstructive pulmonary disease, n (%)	2437 (54)	4480	1221 (54)	2247	1216 (54)	2233	0.002
Cancer (*ICD-9*), n (%)	1179 (26)	4480	594 (26)	2247	585 (26)	2233	0.005
Cerebrovascular disease, n (%)	1281 (29)	4480	645 (29)	2247	636 (28)	2233	0.005
Myocardial infarction, n (%)	793 (18)	4480	396 (18)	2247	397 (18)	2233	0.004
Dementia, n (%)	633 (14)	4480	322 (14)	2247	311 (14)	2233	0.013
Hemiplegia or paraplegia, n (%)	300 (7)	4480	150 (7)	2247	150 (7)	2233	0.002
HIV, n (%)	102 (2)	4480	50 (2)	2247	51 (2)	2233	0.004
Peptic ulcer disease, n (%)	353 (8)	4480	179 (8)	2247	174 (8)	2233	0.006
Rheumatic disease, n (%)	196 (4)	4480	97 (4)	2247	99 (4)	2233	0.006
Metastatic solid tumor, n (%)	230 (5)	4480	115 (5)	2247	115 (5)	2233	<0.001
Baseline eGFR, ml/min per 1.73 m^2, mean (SD)	74.1 (22.7)	3996	74.1 (22.7)	2004	74.1 (22.7)	1992	0.004
Last preadmission BMI, kg/m^2, mean (SD)	30.4 (7.1)	3815	30.4 (7.1)	1914	30.4 (7.2)	1901	0.001
Last preadmission temperature, ° C, mean (SD)	98.0 (0.9)	4204	98.0 (0.8)	2109	98.0 (0.9)	2095	0.006
Last preadmission SBP, mean (SD), mm Hg	131 (19)	4228	131 (19)	2121	131 (19)	2107	0.006
Last preadmission DBP, mm Hg, mean (SD)[a]	76 (11)	4227	76 (11)	2120	76 (11)	2107	0.003
Last preadmission pulse, bpm, mean (SD)	80 (15)	4228	80 (15)	2121	80 (15)	2107	0.002
Last preadmission O_2 saturation, %, mean (SD)	96.4 (2.4)	4099	96.4 (2.4)	2057	96.4 (2.3)	2042	0.006
Last preadmission protein dipstick, n (%)		4480		2247		2233	0.027
Not measured	1896 (42)		957 (43)		939 (42)		
Negative or trace	1794 (40)		887 (39)		907 (41)		
1+	408 (9)		211 (9)		197 (9)		
≥2+	382 (9)		192 (9)		190 (9)		
Last preadmission urine dipstick RBCs, n (%)		4480		2247		2233	0.012
Not measured	1938 (43)		974 (43)		964 (43)		
Negative or trace	1976 (44)		986 (44)		990 (44)		
1+	327 (7)		167 (7)		160 (7)		
≥2+	238 (5)		120 (5)		118 (5)		
Active ACE inhibitor user, n (%)[a]	942 (21)	4480	472 (21)	2247	470 (21)	2233	0.002
Active ARB user, n (%)[b]	485 (11)	4480	243 (11)	2247	242 (11)	2233	<0.001
Active CCB user, n (%)[b]	965 (22)	4480	486 (22)	2247	478 (21)	2233	0.006
Active α-blocker user, n (%)[b]	133 (3)	4480	68 (3)	2247	65 (3)	2233	0.008
Active β-blocker user, n (%)[b]	1173 (26)	4480	586 (26)	2247	586 (26)	2233	0.003
Active K-sparing diuretic user, n (%)[b]	187 (4)	4480	94 (4)	2247	93 (4)	2233	<0.001
Active loop diuretic user, n (%)[b]	506 (11)	4480	252 (11)	2247	254 (11)	2233	0.006
Active thiazide user, n (%)[b]	567 (13)	4480	282 (13)	2247	285 (13)	2233	0.006
Active peripheral vasodilator user, n (%)[b]	119 (3)	4480	59 (3)	2247	60 (3)	2233	0.002
Recent acyclovir fill, n (%)[c]	45 (1)	4480	23 (1)	2247	22 (1)	2233	<0.001
Recent azithromycin fill, n (%)[c]	1254 (28)	4480	627 (28)	2247	627 (28)	2233	0.003
Recent β-lactam fill, n (%)[c]	299 (7)	4480	148 (7)	2247	151 (7)	2233	0.007
Recent cephalosporin fill, n (%)[c]	193 (4)	4480	97 (4)	2247	96 (4)	2233	0.002
Recent hydroxychloroquine fill, n (%)[c]	26 (1)	4480	13 (1)	2247	13 (1)	2233	0.003

(*Continued on following page*)

Table 2 | (Continued)

Demographics and comorbidities	Total $W = 4480$	No. nonmissing	COVID-19–positive $W = 2247$	No. nonmissing	Influenza-positive $W = 2233$	No. nonmissing	SMD
Recent fluoroquinolone fill, n (%)[c]	139 (3)	4480	69 (3)	2247	69 (3)	2233	0.001
Recent H2 blocker fill, n (%)[c]	267 (6)	4480	134 (6)	2247	133 (6)	2233	0.001
Recent NSAID fill, n (%)[c]	596 (13)	4480	297 (13)	2247	299 (13)	2233	0.005
Recent proton pump inhibitor fill, n (%)[c]	1023 (23)	4480	510 (23)	2247	513 (23)	2233	0.006
Recent steroid fill, n (%)[c]	459 (10)	4480	232 (10)	2247	227 (10)	2233	0.005

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; COVID-19, coronavirus disease 2019; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; *ICD-9*, *International Classification of Diseases, Ninth Revision*; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure; SMD, standardized mean difference; *W*, sum of the patient weights.
[a]DBP indicator variable for missingness not included in the logistic regression model because of collinearity with the SBP indicator variable for missingness.
[b]Active user refers to pills on hand at admission.
[c]Recent fill refers to fill within last 104 days.
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 7082 patients was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 4480. SMDs are the absolute difference in means or percentage divided by an evenly weighted pooled SD or difference between groups in number of SDs. For the weighted cohort, all SMDs were <0.1, indicating good balance.

2019 and March 2020, and COVID-19 hospitalizations occurring between February and May 2020.

Patient characteristics

The unweighted descriptions are detailed in Table 1. Patients hospitalized with COVID-19 and influenza were similar in age. Compared with influenza, patients with COVID-19 were more often African American. The prevalence rates of pre-admission diabetes and hypertension were similar between the groups, as was baseline eGFR. Patients with influenza more often had a history of congestive heart failure and chronic obstructive pulmonary disease. Following weighting, the 2 groups were well balanced across demographics and comorbid conditions (Table 2).

Inpatient characteristics

In the unweighted descriptions (Supplementary Tables S2A and B), the mean oxygen saturation trough was 88.6% in the COVID-19 group and 90.7% in the influenza group. Trough oxygen saturations <88% were observed in 26% of patients with COVID-19 and 14% of patients with influenza. Mechanical ventilation was required in 17% of patients with COVID-19 and 3% of those with influenza. Vasopressors were used in 13% of patients with COVID-19 and 2% of those with influenza. Mean peak lactic acid levels were 2.5 mmol/L in the COVID-19 group and 1.9 mmol/L in the influenza group. Mean peak white blood cell counts were 11.2 $\times$ 1000/mm^3 in the COVID-19 group and 9.9 $\times$ 1000/mm^3 in the influenza group.

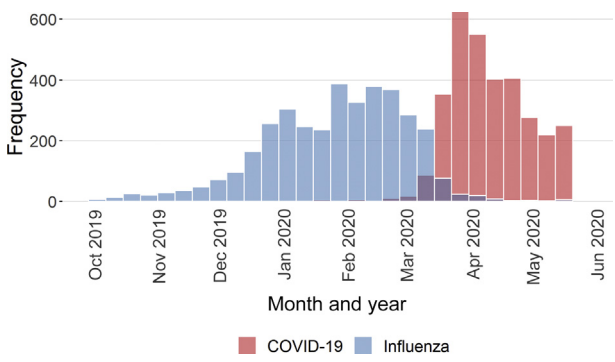

Figure 2 | Distribution of hospitalization dates. Number of hospitalizations for coronavirus disease 2019 (COVID-19) and influenza in each month of the study period. Blue columns denote hospitalizations for influenza. Red columns denote hospitalizations for COVID-19.

After weighting (Table 3), patients with COVID-19 had lower mean oxygen saturation troughs (88.8% vs. 90.9%; $P < 0.001$) and more frequently had oxygen troughs of <88% (25% vs. 13%; $P < 0.001$). The COVID-19 group more often required mechanical ventilation (17% vs. 3%; $P < 0.001$) and vasopressors (13% vs. 1%; $P < 0.001$), and had higher peak lactic acid levels (2.3 mmol/L vs. 1.9 mmol/L; $P < 0.001$) and white blood cell counts (11.2 $\times$ 1000/mm^3 vs. 9.7 $\times$ 1000/mm^3; $P < 0.001$). More patients in the COVID-19 group received vancomycin (24% vs. 15%; $P < 0.001$), whereas the influenza group had more frequent use of steroids (18% vs. 30%; $P < 0.001$).

Kidney outcomes

AKI incidence and severity. In the unweighted descriptions (Supplementary Table S3), the incidence of AKI was 45% in patients with COVID-19 and 27% in those with influenza. In the COVID-19 group, the distribution of AKI was 59%, 15%, and 26% for stages 1, 2, and 3, respectively. The distribution in the influenza group was 82%, 11%, and 7% for stages 1, 2, and 3, respectively. Kidney replacement therapy was required in 12% of patients with AKI in COVID-19 and 2% of those with AKI in influenza.

After weighting (Table 4), the incidence of AKI was higher in COVID-19 than in influenza (41% vs. 29%; $P < 0.001$). The overall distribution of AKI severity was also higher in COVID-19 (60%, 15%, and 26% for stages 1, 2, and 3, respectively, in COVID-19 vs. 82%, 11%, and 6% for stages 1, 2, and 3, respectively, in influenza; $P < 0.001$). More patients in the COVID-19 group required kidney replacement therapy (13% vs. 2%; $P < 0.001$).

Hematuria and proteinuria

Among full cohort. In the unweighted descriptions, hematuria 2+ or higher on urine dipstick occurred in 16% of

Table 3 | Inpatient characteristics of weighted cohorts

Characteristics	COVID-19–positive $W = 2247$	No. nonmissing	Influenza-positive $W = 2233$	No. nonmissing	*P* value
Admission systolic blood pressure, mm Hg, mean (SD)	132 (23)	2224	136 (26)	2230	<0.001
Systolic blood pressure trough, mm Hg, mean (SD)	102 (16)	2224	108 (17)	2230	<0.001
Admission diastolic blood pressure, mm Hg, mean (SD)	76 (13)	2224	78 (14)	2230	<0.001
Diastolic blood pressure trough, mm Hg, mean (SD)	57 (11)	2224	60 (11)	2230	<0.001
Admission pulse, bpm, mean (SD)	92 (19)	2229	96 (20)	2230	<0.001
Admission O_2 saturation, %, mean (SD)	94.4 (5.2)	2182	94.8 (4.1)	2209	0.009
O_2 saturation trough, %, mean (SD)	88.8 (7.4)	2182	90.9 (4.8)	2209	<0.001
O_2 saturation trough <88%, n (%)	553 (25)	2182	289 (13)	2209	<0.001
Mechanical ventilation, n (%)	376 (17)	2247	66 (3)	2233	<0.001
Lactic acid (peak), mmol/L, mean (SD)	2.3 (2.8)	1502	1.9 (1.4)	1252	<0.001
WBC count (peak), 1000/mm^3, mean (SD)	11.2 (8.3)	2242	9.7 (5.5)	2232	<0.001
Proteinuria, n (%)		2247		2233	<0.001
Not measured	819 (36)		873 (39)		
Negative or trace	474 (21)		620 (28)		
1+	389 (17)		359 (16)		
≥2+	564 (25)		381 (17)		
New-onset proteinuria, n (%)	370 (42)	887[a]	254 (28)	907[a]	<0.001
Worsened preexisting proteinuria, n (%)	117 (29)	403[b]	72 (19)	387[b]	<0.001
Hematuria, n (%)		2247		2233	0.066
Not measured	859 (38)		902 (40)		
Negative or trace	808 (36)		780 (35)		
1+	261 (12)		278 (12)		
≥2+	319 (14)		273 (12)		
New-onset hematuria, n (%)	273 (28)	986[a]	207 (21)	990[a]	<0.001
Worsened preexisting hematuria, n (%)	65 (23)	287[b]	55 (20)	278[b]	0.347
Vasopressors, n (%)	282 (13)	2247	33 (1)	2233	<0.001
NSAIDs, n (%)	155 (7)	2247	344 (15)	2233	<0.001
Steroids, n (%)	394 (18)	2247	669 (30)	2233	<0.001
Vancomycin, n (%)	543 (24)	2247	330 (15)	2233	<0.001
β-Lactams, n (%)	451 (20)	2247	386 (17)	2233	0.007
Cephalosporins, n (%)	1128 (50)	2247	780 (35)	2233	<0.001
Length of stay, d, mean (SD)	14.7 (20.4)	2247	5.5 (11.0)	2233	<0.001

COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug; *W*, sum of the patient weights; WBC, white blood cell.
[a]Denominator of patients without preexisting proteinuria (hematuria).
[b]Denominator of patients with preexisting proteinuria (hematuria).
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 7082 (2500 with acute kidney injury [AKI]) patients was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 4480 (1485 with AKI).

patients with COVID-19 and 11% of those with influenza (Supplementary Table S2A). New-onset hematuria, defined as 1+ or higher on urine dipstick and negative or trace blood on preadmission urine dipstick, was observed in 29% of patients with COVID-19 and 18% of patients with influenza. Worsening of preexisting hematuria was observed in 22% of patients with COVID-19 and 18% of patients with influenza. Proteinuria 2+ or higher occurred in 27% of patients with COVID-19 and 15% with influenza. New-onset proteinuria, defined as 1+ or higher on urine dipstick and negative or trace protein on preadmission urine dipstick, was observed in 44% of patients with COVID-19 and 26% of patients with influenza. Worsening proteinuria compared with preadmission baseline was observed in 29% of patients with COVID-19 and 17% of patients with influenza.

In the weighted comparisons (Table 3), proteinuria was more common in patients with COVID-19 compared with influenza. Proteinuria 2+ or higher was observed in 25% of the COVID-19 group compared with 17% of the influenza group ($P < 0.001$). Hematuria 2+ or higher occurred in 14% of patients with COVID-19 and 12% of patients with influenza ($P = 0.066$). Among those with prehospitalization data available, new-onset hematuria and proteinuria were both more common in COVID-19 (hematuria, 28% vs. 21% [$P < 0.001$]; and proteinuria, 42% vs. 28% [$P < 0.001$]). Worsening of baseline hematuria was more common in COVID-19; however, this difference was not statistically significant (23% vs. 20%; $P = 0.347$). Worsening of baseline proteinuria was more common in COVID-19 (29% vs. 19%; $P < 0.001$).

Among patients with AKI. In the unweighted descriptions of patients with AKI, hematuria 2+ or higher on urine dipstick occurred in 25% of patients with COVID-19 and 18% with influenza (Supplementary Table S2B). Proteinuria 2+ or higher occurred in 40% of patients with COVID-19 and 24% with influenza. After weighting, among patients with AKI (Table 5), hematuria 2+ or higher occurred more often in patients hospitalized with COVID-19 compared with influenza (24% vs. 19%; $P = 0.001$). Proteinuria 2+ or higher was more common in patients with COVID-19 compared with patients with influenza (39% vs. 26%; $P < 0.001$).

AKI-related outcomes

In-hospital and 90-day mortality. In the unweighted descriptions of patients with AKI, in-hospital mortality was 32%

Table 4 | Renal and other outcomes among patients with AKI, weighted cohorts

Characteristics	COVID-19–positive $W = 742$	No. nonmissing	Influenza-positive $W = 743$	No. nonmissing	*P* value
Stage of AKI, n (%)[a]		742		743	<0.001
1	442 (60)		613 (82)		
2	110 (15)		84 (11)		
3	190 (26)		46 (6)		
Acute dialysis, n (%)	94 (13)	742	12 (2)	743	<0.001
Dialysis at discharge, n (%)[b]	58 (8)	742	8 (1)	743	<0.001
Peak serum creatinine, mg/dl, mean (SD)	3.10 (2.40)	742	2.15 (1.13)	743	<0.001
Discharge serum creatinine, mg/dl, mean (SD)	2.05 (1.87)	742	1.45 (0.85)	743	<0.001
Death in hospital, n (%)[c]	226 (30)	742	26 (3)	743	<0.001
Stage 1	74 (17)	442	10 (2)	613	<0.001
Stage 2	38 (35)	110	7 (8)	84	<0.001
Stage 3	113 (60)	190	10 (21)	46	<0.001
Death within 90 days of peak serum creatinine, n (%)[c]	263 (35)	742	70 (9)	743	<0.001
Stage 1 AKI	100 (23)	442	46 (7)	613	<0.001
Stage 2 AKI	42 (38)	110	12 (14)	84	<0.001
Stage 3 AKI	120 (63)	190	12 (27)	46	<0.001

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; *W*, sum of the patient weights.
[a]Kidney Disease: Improving Global Outcomes (KDIGO)–modified criteria.
[b]Defined as receiving dialysis within 48 hours of discharge.
[c]Mortality rates stratified by AKI stage and COVID-19 versus influenza diagnosis.
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 2500 patients with AKI was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 1485.

for patients with COVID-19 and 4% for patients with influenza (Supplementary Table S3). In-hospital mortality by AKI stage in the COVID-19 group was 18%, 36%, and 62% for stages 1, 2, and 3, respectively. In-hospital mortality in the influenza group was 2%, 8%, and 24% for stages 1, 2, and 3, respectively. Mortality at 90 days following peak serum creatinine was 38% in COVID-19 group and 10% in influenza group. Mortality at 90 days by AKI stage in the COVID-19 group was 25%, 40%, and 65% for stages 1, 2, and 3, respectively. Mortality at 90 days by AKI stage in the influenza group was 8%, 16%, and 32% for stages 1, 2, and 3, respectively.

The weighted comparisons (Table 4) showed that in-hospital mortality among those with AKI was higher in the COVID-19 group (30% vs. 3%; $P < 0.001$). Higher in-hospital mortality was seen with more severe stages of AKI in both groups, which was more pronounced in patients with COVID-19 versus influenza (17%, 35%, and 60% vs. 2%, 8%, and 21% mortality for stages 1, 2, and 3, respectively; all comparisons, $P < 0.001$). Similarly, mortality at 90 days after peak serum creatinine was higher in the COVID-19 group (35% vs. 9%; $P < 0.001$). Increasing mortality with AKI stage was observed in both groups, with 90-day mortality frequencies of 23%, 38%, and 63% (COVID-19 group) versus 7%, 14%, and 27% (influenza group) for stages 1, 2, and 3, respectively (all comparisons, $P < 0.001$).

Kidney recovery

Kidney recovery analysis was limited to patients who had a prehospital baseline creatinine, with peak serum creatinine occurring at least 90 days before the end of data acquisition, and those who did not require kidney replacement therapy during hospitalization. There were 3 patients in the COVID-19 group whose peak serum creatinine occurred <90 days before the end of data acquisition and were excluded from recovery analysis.

In the unweighted descriptions of those with AKI, the proportions of patients who remained on dialysis at time of discharge were 7% of patients with COVID-19 and 1% of patients with influenza (Supplementary Table S3). The proportions of patients who recovered to within 20% of baseline serum creatinine at 90 days after peak serum creatinine were 57% of the COVID-19 group and 82% of the influenza group (Supplementary Table S4A). Among survivors at 90 days, recovery from AKI was observed in 91% in the COVID-19 group and 91% in the influenza group (Supplemental Table S4B).

In the weighted comparisons of patients with AKI (Tables 4, 6, and 7, Figure 3, and Supplementary Figure S1), patients with COVID-19 had lower rates of recovery from AKI at 90 days following peak serum creatinine compared with patients with influenza (60% vs. 82%; $P < 0.001$). Among those who survived to 90 days following peak serum creatinine, the rates of recovery from AKI were similar (91% in COVID-19 group and 90% in influenza group; $P = 0.494$). Patients with COVID-19 more frequently remained on dialysis at discharge than patients with influenza (8% vs. 1%; $P < 0.001$).

Sensitivity analysis

To control for any potential seasonal, temporal, or surge effects in the early pandemic, we performed a sensitivity analysis that adjusted for admission date as a continuous variable with a 5-knot spline in the propensity score weighting. All covariates, including admission date, were balanced (all standardized mean differences, <0.1). This sensitivity analysis

Table 5 | Inpatient characteristics of patients with AKI, weighted cohorts

Characteristics	COVID-19–positive $W = 742$	No. nonmissing	Influenza-positive $W = 743$	No. nonmissing	*P* value
Admission systolic blood pressure, mm Hg, mean (SD)	129 (25)	731	130 (29)	742	0.549
Systolic blood pressure trough, mm Hg, mean (SD)	99 (17)	731	103 (17)	742	<0.001
Admission diastolic blood pressure, mm Hg, mean (SD)	74 (14)	731	74 (15)	742	0.998
Diastolic blood pressure trough, mm Hg, mean (SD)	55 (11)	731	57 (11)	742	<0.001
Admission pulse, bpm, mean (SD)	93 (20)	734	95 (21)	742	0.144
Admission O_2 saturation, %, mean (SD)	93.5 (6.6)	717	94.7 (4.6)	735	<0.001
O_2 saturation trough, %, mean (SD)	87.0 (8.6)	717	90.5 (5.2)	735	<0.001
O_2 saturation trough <88%, n (%)	253 (35)	717	121 (16)	735	<0.001
Mechanical ventilation, n (%)	255 (34)	742	44 (6)	743	<0.001
Lactic acid (peak), mmol/L, mean (SD)	2.9 (3.9)	605	2.3 (1.8)	488	<0.001
WBC count (peak), 1000/mm^3, mean (SD)	14.6 (9.7)	741	10.9 (7.1)	743	<0.001
Proteinuria, n (%)		742		743	<0.001
Not measured	155 (21)		208 (28)		
Negative or trace	138 (19)		193 (26)		
1+	162 (22)		152 (20)		
≥2+	287 (39)		190 (26)		
New-onset proteinuria, n (%)	158 (67)	236[a]	97 (39)	252[a]	<0.001
Worsened preexisting proteinuria, n (%)	61 (35)	176[b]	40 (23)	170[b]	0.011
Hematuria, n (%)		742		743	0.001
Not measured	166 (22)		222 (30)		
Negative or trace	284 (38)		255 (34)		
1+	117 (16)		122 (16)		
≥2+	176 (24)		143 (19)		
New-onset hematuria, n (%)	149 (49)	303[a]	100 (32)	314[a]	<0.001
Worsened preexisting hematuria, n (%)	36 (34)	105[b]	29 (30)	100[b]	0.434
Vasopressors, n (%)	199 (27)	742	28 (4)	743	<0.001
NSAIDs, n (%)	33 (4)	742	80 (11)	743	<0.001
Steroids, n (%)	192 (26)	742	205 (28)	743	0.391
Vancomycin, n (%)	305 (41)	742	166 (22)	743	<0.001
β-Lactams, n (%)	225 (30)	742	155 (21)	743	<0.001
Cephalosporins, n (%)	476 (64)	742	317 (43)	743	<0.001
Length of stay, d, mean (SD)	19.6 (22.4)	742	7.4 (13.2)	743	<0.001

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug; *W*, sum of the patient weights; WBC, white blood cell.
[a]Denominator of patients without preexisting proteinuria (hematuria).
[b]Denominator of patients with preexisting proteinuria (hematuria).
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 7082 (2500 with AKI) patients was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 4480 (1485 with AKI).

was consistent with the primary analysis, demonstrating robustness to temporal effects. Results from this analysis are detailed in Supplementary Table S5.

DISCUSSION

In this study, we observed a higher incidence and severity of AKI in hospitalized veterans with COVID-19 compared with those with influenza, even after adjusting for baseline demographics and comorbidities. We also found that in-hospital mortality was higher and kidney recovery was lower among hospitalized patients with COVID-19 compared with influenza but similar among survivors. In addition, we found that proteinuria and hematuria occurred more frequently in COVID-19 but were common in both groups.

Prior studies have compared kidney outcomes in COVID-19 with other ill populations. Fisher *et al.* examined

Table 6 | Renal recovery in weighted cohort

Variable	COVID-19–positive $W = 539$	No. nonmissing	Influenza-positive $W = 619$	No. nonmissing	*P* value
AKI recovery within 20% baseline serum creatinine within 90 days, n (%)[a,b]	321 (60)	539	511 (82)	619	<0.001
Stage 1	260 (71)	368	445 (86)	518	<0.001
Stage 2	41 (46)	89	50 (66)	75	<0.001
Stage 3 without dialysis	20 (25)	82	16 (62)	26	<0.001

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; *W*, sum of the patient weights.
[a]Restricted to patients with preadmission baseline serum creatinine, patients with peak serum creatinine occurring at least 90 days before end of data acquisition, and patients who did not require dialysis.
[b]Recovery rates stratified by AKI stage and COVID-19 versus influenza diagnosis.
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 2500 patients with AKI was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 1485.

Table 7 | Renal recovery among survivors at 90 days after peak serum creatinine (weighted cohort)

Variable	COVID-19–positive $W = 441$	No. nonmissing	Influenza-positive $W = 478$	No. nonmissing	*P* value
AKI recovery within 20% baseline serum creatinine within 90 days, n (%)[a,b]	402 (91)	441	430 (90)	478	0.494
Stage 1	325 (95)	343	372 (92)	404	0.111
Stage 2	51 (79)	65	42 (77)	55	0.826
Stage 3 without dialysis	25 (77)	33	15 (78)	19	0.908

AKI, acute kidney injury; COVID-19, coronavirus disease 2019; *W*, sum of the patient weights.
[a]Restricted to patients who survived 90 days after peak serum creatinine, patients with preadmission baseline serum creatinine, patients with peak serum creatinine occurring at least 90 days before end of data acquisition, and patients who did not require dialysis.
[b]Recovery rates stratified by AKI stage and COVID-19 versus influenza diagnosis.
The *W* value can be thought of as the effective number of patients in the weighted cohort created by the matching weights. The entire cohort of 1824 patients with AKI who survived 90 days after peak serum creatinine was used with patients receiving weights greater than 0 and less than or equal to 1, yielding a sum of weights equal to 1169.

AKI in patients with COVID-19 compared with patients hospitalized in the same hospital 1 year prior. They identified risk factors shared between the groups, but also found that AKI was more common and severe with COVID-19.[30] Our study extends on this work by focusing on a more specific control group to show that the incidence and severity of AKI in COVID-19 differ from those in patients with other severe viral respiratory illness, even after adjusting for premorbid demographics and disease. We found that AKI occurred more frequently and was more severe among those with COVID-19. The difference in AKI incidence persisted even after adjusting for baseline characteristics, suggesting that the higher rate of AKI in COVID-19 was not explained by comorbid conditions. We also observed that patients with COVID-19 were more likely to require mechanical ventilation and vasopressors and had higher in-hospital mortality than those with influenza, suggesting that higher severity of illness is likely an important contributor to these differences. These findings are consistent with a recent, smaller study that found similar rates of AKI in COVID-19 and influenza among critically ill patients with similar illness severity.[31] It remains possible that the mechanisms of tubular injury in COVID-19 may be more varied and severe, reflecting more severe systemic inflammatory response, endothelial dysfunction, thrombotic microangiopathy, and direct viral invasion, although the latter remains controversial. A more diverse array of glomerular lesions has also been reported in COVID-19 compared with influenza.[11] Last, a more severe presentation may accrue additional exposures that increase

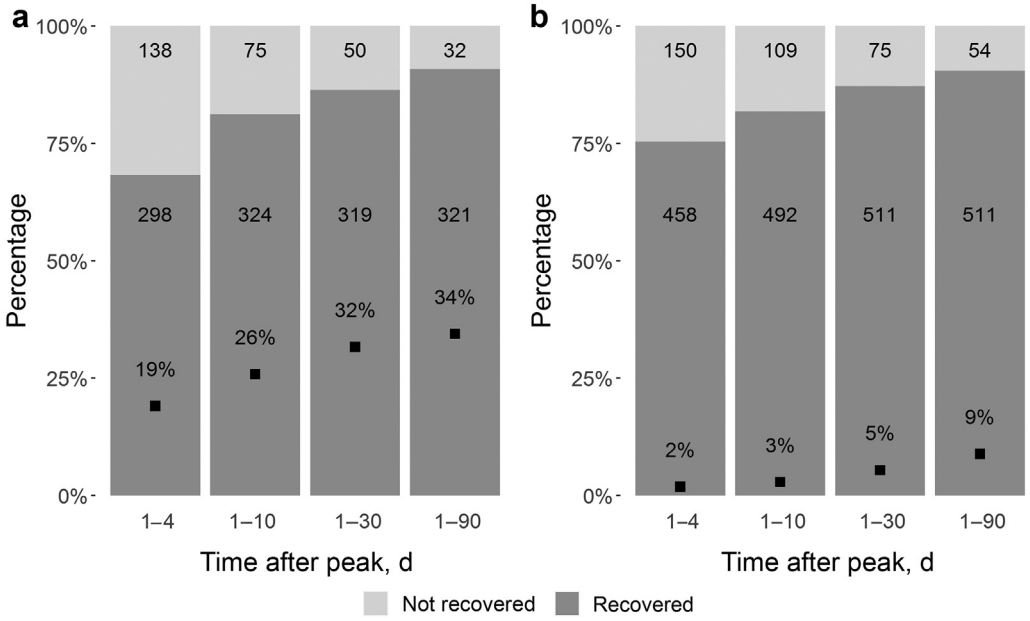

Figure 3 | Recovery from acute kidney injury (AKI) among survivors with (a) coronavirus disease 2019 (COVID-19) and (b) influenza. Proportion of patients achieving recovery from AKI of any stage (excluding patients who received acute dialysis or without a prehospital baseline creatinine) at 4, 10, 30, and 90 days following date of peak serum creatinine. Numbers in each column indicate absolute number of survivors (sum of the patient weights in the weighted cohort) at each time point in recovered (dark gray) and not recovered (light gray) groups. Square in each column denotes mortality rate. Note the higher mortality rates in the COVID-19 group and similar recovery among survivors.

the risk for AKI. We observed that patients with COVID-19 received antibiotics more frequently than those with influenza, with nearly one-quarter receiving vancomycin.

Direct viral invasion of the kidneys has been hypothesized as a mechanism of AKI in COVID-19, with relatively high frequencies of proteinuria and microscopic hematuria,[2] viral RNA, viral protein, and live virus detected in kidney tissue,[19,32,33] as well as collapsing glomerulopathy and other lesions reported.[16,32,34–36] Furthermore, a recent autopsy study correlated the presence of viral RNA in the kidney with clinical outcomes, including AKI.[33] The degree to which the latter accounts for AKI in populations hospitalized with COVID-19 is unclear. We observed that hematuria and proteinuria were also common in influenza. The etiology of these findings may be multifactorial, including prevalent urine abnormalities in this comorbid VA population and possible effects of instrumentation (e.g., foley catheter insertion) during illness. Although these findings suggest that hematuria and proteinuria may not be unique to COVID-19, it remains possible that the higher rates could reflect a direct mechanism of injury due to the SARS-CoV-2 virus. A recent study in patients hospitalized with COVID-19 demonstrated evidence of proximal tubular dysfunction, including tubular proteinuria.[37] Alternatively, the higher rates of hematuria and proteinuria observed in COVID-19 could suggest a similar mechanism of AKI in influenza, with a more severe pathophysiological course in COVID-19. Studies of proteinuria after AKI have demonstrated a dose-response relationship between AKI severity and subsequent proteinuria.[38,39]

Last, we found less recovery from AKI among those with COVID-19 compared with influenza, a difference likely driven by the higher mortality in COVID-19. Although this finding highlights the high mortality associated with AKI in COVID-19, it also provides some optimism for recovery in those who survive the illness, as approximately 90% of survivors of non–dialysis-requiring AKI recovered.

Our findings have important resource implications. We observed a substantial incidence of AKI in influenza, with one-quarter of patients experiencing AKI during hospitalization. It remains to be seen what the impact of mask wearing and social distancing will have on incidence of influenza in the current and future influenza seasons. Regardless, the potential added burden of AKI related to influenza in addition to AKI during hospitalization with COVID-19 could have downstream implications for resource utilization. Goldfarb *et al.* described their experience in the COVID-19 epicenter in the early months of the pandemic, including increased demand for kidney replacement therapy and decreased capacity to provide it, with COVID-19 affecting both their workforce (e.g., dialysis nurses) and dialysis supplies.[40] Given the strain on the health system due to COVID-19, the overall increased burden of kidney disease and its resource allocation due to these illnesses will be important to project. The proportion of patients with AKI who remain dialysis dependent at discharge in our study suggests that this strain on resources may extend to outpatient dialysis centers. Another consideration is the possibility of coinfection with COVID-19 and influenza. Data from the early stages of the pandemic in China showed coinfection rates of COVID-19 with other respiratory viruses were as high as 25%.[41]

The strengths of our study include the use of national data, creatinine-based definitions of AKI, and rigorous attempts to adjust for baseline conditions that might influence AKI risk. Limitations include reduced generalizability to females, lack of histologic data, inability to meaningfully compare certain laboratory measurements, such as ferritin or lactate dehydrogenase, which were infrequently measured in the influenza group, and the possibility of residual confounding. The semiquantitative nature of urine dipstick measurements as well as potential differences in ascertainment and lack of reliable data on the relative use and timing of foley catheter placement between groups also need to be considered in interpreting the urinary findings. Assessment of recovery could have been impacted by ascertainment bias; however, we would suspect the longer length of stay and generally worse prognosis of COVID-19 patients to increase ascertainment in this group and potentially bias our results to the null. Last, we do not know the impact that evolving treatment of COVID-19 or admission thresholds may have had on AKI rates. One recent article examined secular trends of AKI in COVID-19 and showed a decrease in incidence of AKI over time, although it appears that severe AKI and need for dialysis remained substantial.[42]

In conclusion, we observed higher incidence and severity of AKI and higher mortality in veterans hospitalized with COVID-19 compared with influenza. These findings may be driven, at least in part, by severity of illness. Further studies to determine whether AKI in COVID-19 is due to a distinct pathophysiology are needed. In addition, among those who survived to 90 days, recovery from AKI was similarly high among patients infected with either illness. The relatively high incidence of AKI in both illnesses provides important information on the anticipated burden on the kidney health of veterans, and similarly ill populations, and their care providers.

DISCLOSURE

EDS reports consulting for Akebia Therapeutics, Inc., in April 2019; honorarium for an invited education talk at the DaVita Annual Physician Leadership Conference in February 2019; royalties as an author for UptoDate, Inc.; and serves on the editorial board for the *Clinical Journal of the American Society of Nephrology*. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

EDS, MEM, SKP, AMP, RAG, AMH, SCS, JPA, and BCB designed the study; SKP, JD, AJV, and MEM collected the data; AMP, RAG, EDS, MEM, SKP, AMH, SCS, JPA, and BCB analyzed the data; AMP and AJV made the figures; BCB, EDS, AMP, RAG, SKP, MEM, and SCS drafted the initial manuscript, which was additionally revised by all authors. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Supplementary definitions.

Table S2A. Inpatient characteristics, unweighted cohort.

Table S2B. Inpatient characteristics of patients with AKI, unweighted cohort.

Table S3. Renal and other outcomes among patients with AKI, unweighted cohort.

Table S4A. Renal recovery overall, unweighted cohort.

Table S4B. Renal recovery among survivors (unweighted cohort).

Table S5. Sensitivity analysis of AKI incidence and severity adjusted for admission date.

Figure S1. Recovery from stage 2 or 3 AKI.

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