Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Kidney Disease With Outcomes in COVID-19: Results From the American Heart Association COVID-19 Cardiovascular Disease Registry

Anjali Rao, MD; Sagar Ranka, MD; Colby Ayers, MS; Nicholas Hendren, MD; Anna Rosenblatt, MD; Heather M. Alger, PhD; Christine Rutan, CPHQ; Wally Omar, MD; Rohan Khera, MD, MS; Kamal Gupta, MD; Purav Mody, MD; Christopher DeFilippi, MD; Sandeep R. Das, MD, MPH; S. Susan Hedayati, MD, MSc; James A. de Lemos, MD

BACKGROUND: Emerging evidence links acute kidney injury (AKI) in patients with COVID-19 with higher mortality and respiratory morbidity, but the relationship of AKI with cardiovascular disease outcomes has not been reported in this population. We sought to evaluate associations between chronic kidney disease (CKD), AKI, and mortality and cardiovascular outcomes in patients hospitalized with COVID-19.

METHODS AND RESULTS: In a large multicenter registry including 8574 patients with COVID-19 from 88 US hospitals, data were collected on baseline characteristics and serial laboratory data during index hospitalization. Primary exposure variables were CKD (categorized as no CKD, CKD, and end-stage kidney disease) and AKI (classified into no AKI or stages 1, 2, or 3 using a modification of the Kidney Disease Improving Global Outcomes guideline definition). The primary outcome was all-cause mortality. The key secondary outcome was major adverse cardiac events, defined as cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, new-onset nonfatal heart failure, and nonfatal cardiogenic shock. CKD and end-stage kidney disease were not associated with mortality or major adverse cardiac events after multivariate adjustment. In contrast, AKI was significantly associated with mortality (stage 1 hazard ratio [HR], 1.72 [95% CI, 1.46–2.03]; stage 2 HR, 1.83 [95% CI, 1.52–2.20]; stage 3 HR, 1.69 [95% CI, 1.44–1.98]; versus no AKI) and major adverse cardiac events (stage 1 HR, 2.17 [95% CI, 1.74–2.71]; stage 2 HR, 2.70 [95% CI, 2.07–3.51]; stage 3 HR, 3.06 [95% CI, 2.52–3.72]; versus no AKI).

CONCLUSIONS: This large study demonstrates a significant association between AKI and all-cause mortality and, for the first time, major adverse cardiovascular events in patients hospitalized with COVID-19.

Key Words: acute kidney injury ■ chronic kidney disease ■ COVID-19 ■ mortality

Chronic kidney disease (CKD) and acute kidney injury (AKI) are common among hospitalized patients, particularly those with critical illness. Both CKD and AKI have been shown to be significantly associated with an increased risk of mortality among patients hospitalized for a spectrum of cardiac and noncardiac illnesses.[1–4] For example, among patients with acute myocardial infarction (MI) or heart failure, CKD and AKI demonstrated a dose-dependent association with mortality, with increased risk seen even for individuals with mild CKD or AKI.[2,3] Data among critically ill patients with acute noncardiac illnesses, such as sepsis, are not as consistent, with some studies showing an association and others reporting that only severe AKI and need for dialysis are associated with increased risk of adverse outcomes.[3,4]

Correspondence to: James de Lemos, MD, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Ste. E5. 7528, Dallas, TX 75390-8830. E-mail: james.delemos@utsouthwestern.edu

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This large, multicenter, retrospective study demonstrates a significant association between acute kidney injury and mortality in patients hospitalized with COVID-19.
- This study is the first to demonstrate a significant association between acute kidney injury and major adverse cardiovascular events in COVID-19, even after multivariate adjustment.

What Are the Clinical Implications?

- In patients with COVID-19, care should be taken to minimize use of therapies that may cause or contribute to acute kidney injury, including iodinated contrast and nonsteroidal anti-inflammatory drugs.
- Additional studies are needed to identify treatment strategies to prevent acute kidney injury or modify outcomes after acute kidney injury in patients hospitalized with COVID-19 and other critical medical illnesses.

Nonstandard Abbreviations and Acronyms

AKI	acute kidney injury
ESKD	end-stage kidney disease
MACE	major adverse cardiac event

Patients with kidney disease have suppressed innate and adaptive immunity, which may contribute to increased infection risk.[5] COVID-19 infection has been reported to be more severe among patients with underlying CKD.[6,7] Moreover, severe AKI has been reported in prior respiratory viral outbreaks, such as H1N1 (hemagglutinin type 1 and neuraminidase type 1) influenza, where it was associated with increased 30-day mortality.[8] Prior studies in patients with community-acquired pneumonia demonstrate the increased morbidity and mortality associated with AKI during the hospitalization.[9–12] A significant association has also been identified between AKI and adverse cardiovascular events, as suggested in a meta-analysis by Odutayo and colleagues.[13] AKI was also frequently reported in early series of patients with COVID-19.[14–20] More recent larger US cohorts have reported AKI incidences as high as 50%, especially among patients requiring intensive care.[21,22] AKI correlated with illness severity, and among patients with AKI, about 20% required dialysis, half of whom died in the hospital.[22] To date, most studies of the associations of CKD and AKI in COVID-19 have been limited by small sample size, inclusion of few centers, or a focus on critically ill patients. Moreover, to our knowledge, there are no published studies that investigated the association of kidney diseases with major adverse cardiac events (MACEs), which disproportionately affects patients with CKD. We therefore sought to evaluate the associations of CKD and AKI with a primary outcome of all-cause mortality and secondary outcomes of MACEs, venous thromboembolic events, and bleeding events in a large multicenter registry of US patients hospitalized with COVID-19. We also evaluated associations of CKD and AKI with baseline and peak blood inflammatory and cardiac biomarkers, including C-reactive protein, interleukin-6, BNP (B-type natriuretic peptide), and NT-proBNP (N-terminal pro–brain natriuretic peptide). Our main hypothesis was that both AKI and CKD would be associated with MACEs, thromboembolic events, and all-cause mortality.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the American Heart Association's (AHA) COVID-19 cardiovascular disease (CVD) registry team at qualityresearch@heart.org.

Study Population

The AHA's COVID-19 CVD registry is a voluntary quality improvement registry that enrolls patients with active COVID-19 from participating centers. At the time of first data release (July 22, 2020), 88 US hospitals were contributing data. Trained data abstractors are instructed to collect data from consecutive patients with hospitalized COVID-19 infection. Data are entered into an electronic case record form, with real-time error checking and data quality checks. Information is collected on >200 variables and includes demographics, cardiovascular risk factors and medical comorbidities, medications, presenting symptoms and clinical findings, and serial laboratory data. Outcomes are recorded for the duration of the hospital stay. Informed consent is not required as there is no participant interaction. The registry is designed for quality improvement and only collects a limited data set, with current analyses performed on a deidentified data set on the AHA's Precision Medicine Platform (https://precision.heart.org). Data collection is performed by Quintiles and IMS Health, Incorporated, and data coordination is provided by the Duke Clinical Research Institute. The registry was

approved by the Duke University Institutional Review Board. The design and structure of the registry have been previously reported.[23–25]

Primary Exposures

CKD was defined from the case record form using data fields for CKD and currently on dialysis and was categorized as no CKD, CKD not on dialysis, or end-stage kidney disease (ESKD) for those on dialysis. Sites were instructed to code CKD if there was a history of physician-diagnosed kidney insufficiency or chronic kidney failure or if a prior serum creatinine was greater than 2.0 mg/dL. Current dialysis was defined as chronic hemodialysis or peritoneal dialysis.

AKI was defined using 2 definitions. Patients with discordant classifications using the 2 definitions were classified into the higher category. The AKI definitions excluded patients with ESKD on chronic hemodialysis before admission.

1. For patients without CKD or chronic dialysis:
   - Stage 1: first documented serum creatinine 1.5 to 1.9 mg/dL
   - Stage 2: first documented serum creatinine 2 to 2.9 mg/dL
   - Stage 3: first documented serum creatinine ≥3.0 mg/dL
2. For patients with at least 2 recorded serum creatinine measures, AKI was defined by change from baseline to peak creatinine. Classifications were defined based on Kidney Disease Improving Global Outcomes guidelines:[26]
   - Stage 1: increase in serum creatinine to 1.5 to 1.9× baseline creatinine in 7 days or by ≥0.3 mg/dL in 48 hours
   - Stage 2: increase in serum creatinine to 2 to 2.9× baseline creatinine in 7 days
   - Stage 3: increase in serum creatinine to ≥3× baseline creatinine in 7 days, an increase in creatinine to an absolute value of ≥4.0 mg/dL, or initiation of dialysis

The 2 approaches to diagnosing AKI were necessary as serum creatinine before admission was not available. Moreover, because patients were admitted on average 6 days into the course of their COVID illness, elevation of the admission creatinine may have reflected AKI present on admission.

Study Outcomes

The primary prespecified outcome was all-cause mortality during index hospitalization for COVID-19. The secondary prespecified outcomes were MACEs, venous thromboembolic events (deep vein thrombosis or pulmonary embolism), and bleeding events. MACE was defined as cardiovascular death, nonfatal stroke, nonfatal MI, new-onset nonfatal heart failure, and nonfatal cardiogenic shock. End points were collected by abstractors at the sites and were not adjudicated. We also evaluated associations of CKD and AKI with baseline and peak blood biomarkers, including C-reactive protein, interleukin-6, BNP, and NT-proBNP.

Statistical Analysis

Patients were stratified into CKD categories (no CKD, nondialysis CKD, and ESKD) and separately into AKI categories (no AKI or stage 1, stage 2, or stage 3 AKI). Baseline characteristics were reported using median and interquartile range or number (percentage) and compared across previously defined CKD or AKI categories using trend tests. Multivariate logistic regression was used to identify factors associated with the development of AKI among patients with COVID-19, excluding patients on chronic dialysis before admission. Variables were selected based on clinical plausibility and significant associations ($P<0.05$) in univariate analyses. All AKI categories were collapsed together for this analysis.

Therapies administered during hospitalization were compared across CKD and AKI categories, including COVID-related treatments and participation in clinical trials. The cumulative incidence of in-hospital all-cause mortality was compared across CKD and AKI categories using the log-rank test. Cox proportional hazards regression models were created for in-hospital mortality, adjusted for age, sex, race/ethnicity, insurance status, smoking, hypertension, diabetes mellitus, prior CVD (coronary artery disease, heart failure, atrial fibrillation, stroke), with robust standard errors used to account for clustering of patients within enrolling sites. Nonfatal events were evaluated in a similar manner in models that account for the competing risk of death. A similar approach was used to evaluate the association of AKI categories with outcomes, except that models also adjusted for CKD (present/absent), and the mortality model additionally adjusted for in-hospital complications including cardiac arrest, shock, heart failure, and MI. Patients with ESKD on chronic hemodialysis before admission were excluded from the analyses of the association of AKI categories with outcomes. Stratified analyses were performed in subgroups defined by in-hospital shock or cardiac arrest and in-hospital ventilator use. A sensitivity analysis was performed to determine if associations of AKI categories with outcomes differed based on the 2 methods for defining AKI. All analyses were performed using SAS version 9.4 (Cary, NC),

Table 1. Baseline Characteristics and Crude Outcomes Stratified by CKD and ESKD on Hemodialysis

Clinical Characteristic	No CKD, N=7416	Nondialysis CKD, N=841	ESKD on Chronic Dialysis, N=335	*P* Value
Age, y	61 (48–73)	74 (63–83)	66 (53–74)	<0.0001
Weight, kg	82 (69–99)	79 (67–95)	73 (62–87)	<0.0001
Male	4045 (54.5)	505 (60.1)	204 (60.9)	0.0002
Race/ethnicity				
White	2365 (31.9)	342 (40.7)	60 (17.9)	0.29
Black	1638 (22.1)	254 (30.2)	118 (35.2)	<0.0001
Hispanic	2302 (31)	165 (19.6)	127 (37.9)	<0.0001
Other* race	486 (6.6)	31 (3.7)	16 (4.8)	.0004
Smoking	465 (6.3)	58 (6.9)	21 (6.3)	0.57
Hypertension	4102 (55.3)	713 (84.8)	284 (84.8)	<0.0001
Dyslipidemia	2402 (32.4)	481 (57.2)	147 (43.9)	<0.0001
Diabetes mellitus	2497 (33.7)	455 (54.1)	214 (63.9)	<0.0001
Prior MI	264 (3.6)	88 (10.5)	31 (9.3)	<0.0001
Prior CHF	550 (7.4)	291 (34.6)	113 (33.7)	<0.0001
Prior stroke	462 (6.2)	132 (15.7)	57 (17)	<0.0001
Prior CVD	1193 (16.1)	410 (48.8)	167 (49.9)	<0.0001
ACEI on admission	1109 (33.3)	136 (22.2)	47 (17.9)	<0.0001
ARB on admission	818 (24.5)	114 (18.6)	51 (19.4)	0.0005
Time from symptom onset to presentation, days	6 (3–9)	3.5 (1–7)	2.5 (1–6)	<0.0001
Enrollment in clinical trial	687 (9.3)	87 (10.5)	19 (5.7)	0.68
In-hospital COVID therapy				
Corticosteroids, oral	1512 (21.1)	211 (27.0)	72 (22.0)	0.004
Hydroxychloroquine	244 (3.3)	35 (4.2)	3 (0.9)	0.77
Remdesivir	619 (8.4)	56 (6.8)	2 (0.6)	<0.0001
Symptoms				
Confusion	681 (9.4)	167 (20.1)	51 (15.7)	<0.0001
Fatigue	1773 (24.5)	209 (25.2)	74 (22.8)	0.95
Fever/chills	4702 (65)	441 (53.1)	199 (61.4)	<0.0001
Headache	716 (9.9)	44 (5.3)	9 (2.8)	<0.0001
Anosmia	302 (4.2)	21 (2.5)	5 (1.5)	0.0015
Myalgias	1594 (22)	124 (14.9)	48 (14.8)	<0.0001
Nasal congestion	376 (5.2)	40 (4.8)	8 (2.5)	0.11
Nausea	1994 (27.6)	217 (26.1)	88 (27.2)	0.43
Shortness of breath	4389 (60.7)	462 (55.6)	169 (52.2)	<0.0001
Sore throat	512 (7.1)	25 (3)	13 (4)	<0.0001
Biomarkers (baseline)†				
Troponin (N=4938), ng/L	0 (0–50)	40 (0–180)	100 (30–400)	<0.0001
C-reactive protein (N=5104), mg/L	4.7 (1.1–10.0)	6.5 (1.8–10.0)	6.3 (1.6–10.0)	<0.0001
Creatinine (N=8326), mg/dL	1.0 (0.8–1.2)	2.0 (1.4–3.1)	7.1 (4.7–10.3)	<0.0001
Interleukin-6 (N=1162) pg/mL	18.5 (5.0–59.0)	28.2 (7.0–100.1)	35.5 (10.2–104.5)	0.003
NT-proBNP (N=1951), pg/mL	186 (50–840)	1742 (418–6100)	30958 (7162–65762)	<0.0001
BNP (N=1797), pg/mL	48 (18–165)	177 (57–673)	872 (214–2872)	<0.0001
Biomarkers (peak)†				
Troponin (N=2222), ng/L	10 (0–200)	100 (10–500)	200 (100–1200)	<0.0001
C-reactive protein (N=3669), mg/L	6.6 (1.7–10.0)	9.1 (2.9–10.7)	8.7 (3.2–10.09)	<0.0001

(*Continued*)

Table 1. Continued

Clinical Characteristic	No CKD, N=7416	Nondialysis CKD, N=841	ESKD on Chronic Dialysis, N=335	*P* Value
Creatinine (N=6518), mg/dL	1.6 (0.8–1.3)	3.3 (1.5–3.9)	9.0 (6.2–11.3)	<0.0001
Interleukin-6 (N=883), pg/mL	29.0 (6.0–114.7)	41.7 (13.0–89.7)	18.90 (5.0–72.0)	0.72
NT-proBNP (N=773), pg/mL	275 (72–1224)	2333 (538–8270)	38221 (17775–70000)	<0.0001
BNP (N=479), pg/mL	101 (34–351)	377 (135–650)	534 (325–3803)	<0.0001
Crude outcomes				
Death	1231 (16.6)	252 (30)	96 (28.7)	<0.0001
Cardiac arrest	394 (5.4)	65 (7.9)	33 (9.9)	<0.0001
MACE	581 (7.8)	92 (10.9)	36 (13.7)	<0.0001
In-hospital shock	870 (12.3)	144 (18.7)	57 (17.7)	<0.0001
New initiation of RRT during hospitalization	250 (3.4)	75 (9.1)	11 (3.3)	<0.0001
Length of stay, d	5.7 (3.5–10.7)	6.7 (3.87–12.3)	7.7 (3.9–13.1)	<0.0001
ICU admission	2038 (27.7)	276 (33.4)	118 (35.4)	<0.0001
Days in ICU	8 (4–15)	5 (2–11)	4 (2–9)	0.001
Ventilator use	1507 (20.5)	189 (22.9)	79 (23.7)	0.04
Ventilator days	8 (3–14)	7 (3–12)	4 (2–10)	0.0003
Thrombotic events	250 (3.4)	22 (2.7)	7 (2.1)	0.10
Deep vein thrombosis	169 (2.3)	18 (2.2)	5 (1.5)	0.47
Pulmonary embolism	109 (1.5)	5 (0.6)	2 (0.6)	0.02
Stroke	81 (1.1)	13 (1.6)	5 (1.5)	0.19
Clinical bleeding requiring transfusion	193 (2.6)	36 (4.4)	21 (6.4)	<0.0001

Data are provided as number (percentage) or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; ESKD, end-stage kidney disease; ICU, intensive care unit; MACE, major adverse cardiac event; MI, myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic peptide; and RRT, renal replacement therapy.

*Other includes Asian, American Indian, Native Hawaiin or Pacific Islander.

†Biomarkers were not available in the full study sample.

and statistical significance was determined by a 2-sided *P*-value <0.05.

RESULTS

Chronic Kidney Disease

Baseline Characteristics and Biomarkers

The overall cohort was composed of 8574 patients. Of these patients, 7416 had no CKD, 841 had nondialysis CKD, and 335 had ESKD. Overall, individuals with nondialysis CKD were older, more likely to be Black patients, and had a higher prevalence of hypertension, dyslipidemia, diabetes mellitus, prior stroke, and prior CVD (*P*<0.0001 for each). Patients with ESKD on chronic dialysis were younger compared with those with nondialysis CKD. Patients with nondialysis CKD tended to be admitted to the hospital for COVID-19 after a shorter symptom duration compared with those without CKD (Table 1). There was no significant difference in enrollment in COVID-19 clinical trials among the 3 groups. Notably, patients with nondialysis CKD or ESKD had different symptom profiles on presentation (as compared with no CKD), with a higher proportion reporting confusion. The CKD and ESKD groups also had higher admission levels of C-reactive protein, IL-6 (interleukin-6), BNP, and NT-proBNP and reached higher peak levels of these biomarkers during the hospitalization compared with those without CKD, with the exception of IL-6, which showed similar peak levels across groups (Table 1).

Primary and Secondary Outcomes

In unadjusted analyses, prior nondialysis CKD or ESKD on chronic dialysis were associated with significantly higher rates of in-hospital all-cause mortality as well as MACEs and major in-hospital complications such as cardiac arrest, shock, intensive care unit admission, and clinical bleeding requiring transfusion (log-rank *P*<0.0001 for each; Table 1). After multivariate adjustment, however, the associations of nondialysis CKD and ESKD on chronic dialysis with mortality were attenuated and no longer significant (hazard ratio [HR], 1.15 [95% CI, 0.99–1.33], and HR, 1.17 [95% CI, 0.93–1.47], respectively;

Figure 1). Similarly, with multivariate adjustment, the association of nondialysis CKD and ESKD on chronic dialysis with MACEs was no longer significant (Figure 1). The multivariate analyses demonstrated a significant inverse association between ESKD and thromboembolic complications (HR, 0.31; 95% CI, 0.11–0.88; Figure 1).

Acute Kidney Injury

Baseline Characteristics and Biomarkers

Overall, 8326 (97%) patients had a baseline creatinine value recorded and 6476 (77%) had at least 2 measurements recorded. There were 8121 patients with a valid AKI grouping. After exclusion of participants with ESKD at baseline who were not eligible for the AKI analyses, there were 6011 without AKI, 902 with stage 1 AKI, 431 with stage 2 AKI, and 777 with stage 3 AKI. Individuals with AKI tended to be older and were more likely to be men and of Black race ($P<0.0001$ for each; Table 2). In addition, there was a greater prevalence of hypertension, dyslipidemia, diabetes mellitus, prior stroke, prior CVD, and CKD among individuals with higher AKI stages compared with those without AKI ($P<0.0001$ for each; Table 2). In a multivariate logistic regression model, older age, male sex, Black race, history of diabetes mellitus or hypertension, in-hospital shock or cardiac arrest, and mechanical ventilation were significantly associated with AKI (Table 3).

Time from symptom onset to presentation was shorter among individuals with versus without AKI ($P<0.0001$; Table 2). Compared with those without AKI, individuals in the AKI groups reported symptoms of confusion more often, whereas constitutional symptoms, headache, anosmia, myalgias, nasal congestion, sore throat, and nausea were less common ($P<0.0001$ for each; Table 2). The cardiovascular and inflammatory biomarkers on presentation and at peak during the hospitalization were significantly higher in the AKI groups compared with the group without AKI ($P<0.0001$ for each), but did not differ between

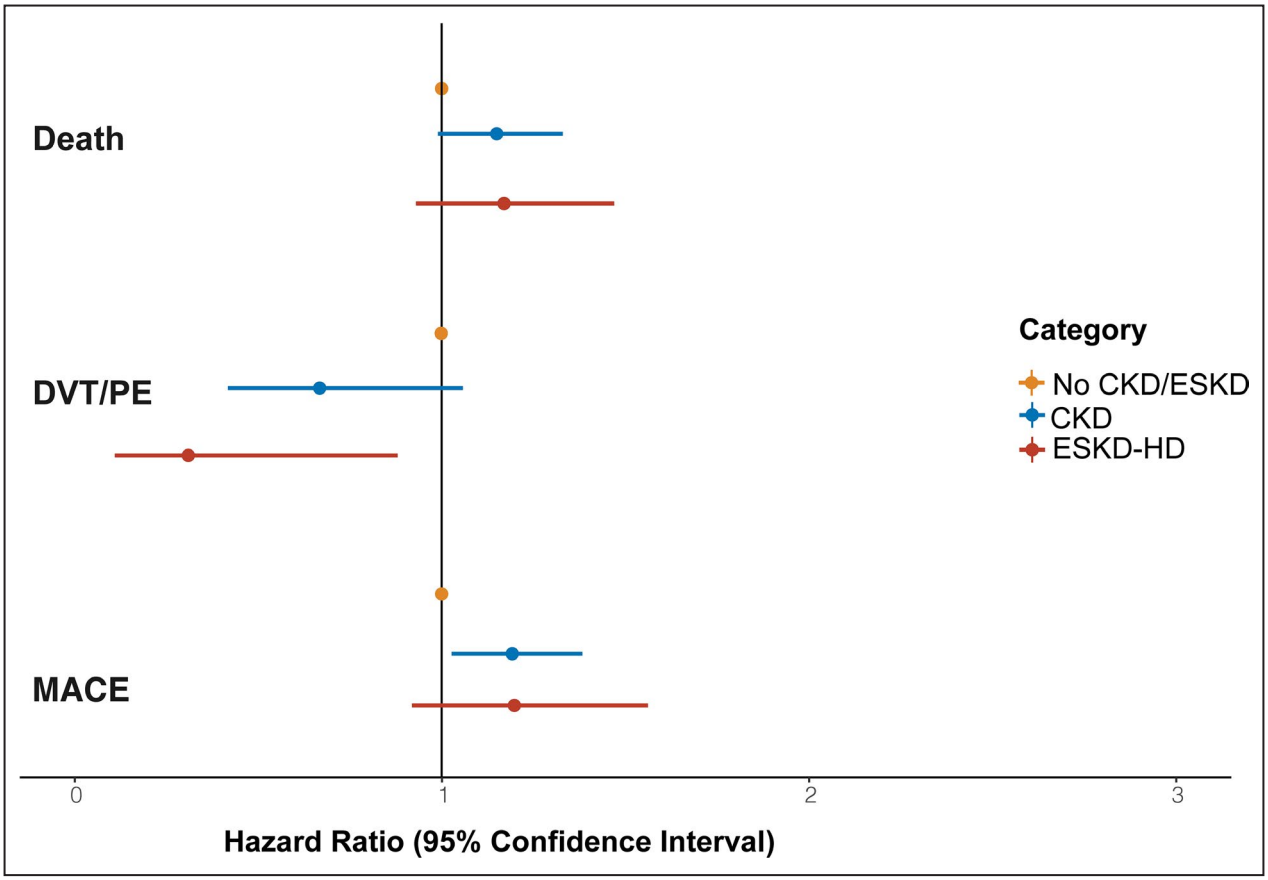

Figure 1. Forest plot of multivariate adjusted primary and key secondary outcomes by CKD stage.
Plots represent the hazard ratio with corresponding 95% CI for the corresponding outcome by CKD stage. Yellow represents the "end-stage kidney disease on chronic dialysis" group, blue represents the "nondialysis CKD" group, and red represents the "no CKD or ESRD" group. Multivariate models included adjustment for age, sex, race/ethnicity, insurance status, smoking, diabetes mellitus, hypertension, and prior cardiovascular disease (coronary artery disease, heart failure, atrial fibrillation, stroke). CKD indicates chronic kidney disease; DVT, deep vein thrombosis; ESKD, end stage kidney disease not on dialysis; ESKD-HD, end stage kidney disease on dialysis; MACE, major adverse cardiovascular event; and PE, pulmonary embolism.

Table 2. Baseline Characteristics and Crude Outcomes Stratified by AKI Stage

Clinical Characteristic	No AKI, N=6011	AKI Stage 1, N=902	AKI Stage 2, N=431	AKI Stage 3, N=777	*P* Value
Age, y	60 (47–73)	69 (58–79)	71 (62–82)	65 (55–74)	<0.0001
Weight, kg	82 (69–98)	79 (67–99)	80 (68–96)	83 (69–102)	0.80
Male	3189 (53.1)	564 (62.5)	272 (63.1)	504 (64.9)	<0.0001
Race/ethnicity					
White	1958 (32.6)	312 (34.6)	135 (31.3)	210 (27.0)	0.08
Black	1229 (20.5)	264 (29.3)	126 (29.2)	249 (32.1)	<0.0001
Hispanic	1929 (32.1)	217 (24.1)	103 (23.9)	217 (27.9)	<0.0001
Other* race	391 (6.5)	46 (5.1)	30 (7.0)	43 (5.5)	0.187
Smoking	377 (6.3)	56 (6.2)	31 (7.2)	50 (6.4)	0.70
Hypertension	3177 (52.9)	689 (76.4)	343 (79.6)	565 (72.7)	<0.0001
Dyslipidemia	1938 (32.2)	403 (44.7)	196 (45.5)	317 (40.8)	<0.0001
Diabetes mellitus	1921 (32)	416 (46.1)	229 (53.1)	374 (48.1)	<0.0001
Prior MI	235 (3.9)	51 (5.7)	28 (6.5)	34 (4.4)	0.0096
Prior CHF	501 (8.3)	168 (18.6)	66 (15.3)	94 (12.1)	<0.0001
Prior stroke	364 (6.1)	104 (11.5)	45 (10.4)	73 (9.4)	<0.0001
Prior CVD	1001 (16.7)	281 (31.2)	119 (27.6)	187 (24.1)	<0.0001
Prior CKD	489 (8.1)	206 (22.8)	23 (5.3)	100 (12.9)	<0.0001
Time from symptom onset to presentation, days	6 (3–9)	4 (2–7)	5 (2–8)	5 (2–9)	<0.0001
Enrollment in clinical trial	592 (9.9)	70 (7.8)	27 (6.3)	54 (7)	0.0002
In-hospital medications					
Corticosteroids	1099 (18.6)	227 (25.5)	119 (27.9)	271 (35.2)	<0.0001
Hydroxychloroquine	5843 (97.3)	873 (96.9)	411 (95.6)	735 (94.7)	0.0003
Remdesivir	553 (9.2)	47 (5.2)	22 (5.1)	33 (4.3)	<0.0001
Symptoms					
Confusion	490 (8.3)	145 (16.5)	87 (21.4)	112 (14.7)	<0.0001
Fatigue	1492 (25.3)	216 (24.6)	91 (22.4)	187 (24.5)	0.31
Fever/chills	3943 (66.8)	528 (60.2)	206 (50.7)	454 (59.6)	<0.0001
Headache	650 (11)	45 (5.1)	19 (4.7)	37 (4.9)	<0.0001
Anosmia	276 (4.7)	18 (2.1)	10 (2.5)	17 (2.2)	<0.0001
Myalgias	1400 (23.7)	126 (14.4)	52 (12.8)	124 (16.3)	<0.0001
Nasal congestion	341 (5.8)	22 (2.5)	8 (2)	32 (4.2)	<0.0001
Nausea	1723 (29.2)	218 (24.9)	90 (22.2)	180 (23.6)	<0.0001
Shortness of breath	3593 (60.9)	507 (57.8)	229 (56.4)	475 (62.3)	0.30
Sore throat	459 (7.8)	29 (3.3)	10 (2.5)	35 (4.6)	<0.0001
Biomarkers, baseline†					
Troponin (N=4779), ng/L	0 (0–30)	30 (0–200)	45 (0–200)	40 (0–220)	<0.0001
C-reactive protein (N=4892), mg/L	4.5 (1.12–10.0)	5.7 (1.4–10.0)	7.9 (1.7–10.2)	6.1 (1.4–10.0)	<0.0001
Creatinine (N=8052), mg/dL	0.9 (0.7–1.1)	1.7 (1.5–1.9)	2.2 (2.0–2.5)	3.0 (1.2–5.1)	<0.0001
Interleukin-6 (N=1102), pg/mL	15.5 (5–45.8)	18.6 (6–79)	41.3 (20–111)	47.3 (12–152.9)	<0.0001
NT-proBNP (N=1832), pg/mL	139 (41–668)	1112 (218–3935)	1225 (299–3860)	1461 (391–6089)	<0.0001
BNP (N=1735), pg/mL	45 (18–164)	126 (36–457)	108 (32–282.5)	112 (33–442)	<0.0001
Biomarkers, peak†					
Troponin (N=2213), ng/mL	10 (0–100)	100 (0–700)	110 (5–805)	100 (10–900)	<0.0001
C-reactive protein (N=3657), mg/L	6.6 (1.55–9.99)	8.1 (2.2–10.0)	9.1 (2.4–11.5)	10.0 (2.6–17.1)	<0.0001
Creatinine (N=6517), mg/dL	1.1 (0.7–1.1)	3.0 (1.4–2.7)	2.6 (1.8–2.9)	7.0 (2.6–6.9)	<0.0001

(*Continued*)

Table 2. Continued

Clinical Characteristic	No AKI, N=6011	AKI Stage 1, N=902	AKI Stage 2, N=431	AKI Stage 3, N=777	*P* Value
Interleukin-6 (N=881), pg/mL	23.00 (5.8–83.4)	38.6 (10.0–148.5)	30.5 (8.6–123.3)	86.0 (22.0–228.4)	<0.0001
NT-proBNP (N=772), pg/mL	215 (57–1014)	1223 (208–5278)	847.5 (354–4702)	1490 (441–6000)	<0.0001
BNP (N=478), pg/mL	91 (32–351)	208 (90–582)	205.95 (34–1577)	200 (74–507)	<0.0001
Crude outcomes					
Death	611 (10.2)	280 (31.1)	166 (38.6)	379 (48.9)	<0.0001
Cardiac arrest	179 (3)	86 (9.6)	57 (13.3)	147 (19)	<0.0001
MACE	279 (4.6)	122 (13.5)	81 (18.8)	203 (26.1)	<0.0001
In-hospital shock	384 (6.7)	161 (18.2)	120 (28.6)	355 (46.6)	<0.0001
New initiation of RRT during hospitalization	16 (0.3)	5 (0.6)	11 (2.6)	283 (36.5)	<0.0001
Length of stay, days	5.6 (3.4–9.7)	7.0 (3.9–13.1)	7.0 (3.8–13.7)	9.7 (5–18.2)	<0.0001
ICU admission	1298 (21.6)	350 (38.8)	206 (47.8)	482 (62.0)	<0.0001
Days in ICU	6 (3–14)	7 (3–14)	9 (3–18)	11 (4–18)	0.02
Crude outcomes					
Ventilator use	810 (13.5)	276 (30.6)	180 (41.9)	444 (57.2)	<0.0001
Ventilator days	7 (3–13)	7 (3–12)	7 (3–13)	9 (5–16)	<0.0001
Thrombotic events	167 (2.8)	38 (4.2)	16 (3.7)	55 (7.1)	<0.0001
Deep vein thrombosis	114 (1.9)	23 (2.6)	13 (3)	40 (5.2)	<0.0001
Pulmonary embolism	70 (1.2)	16 (1.8)	5 (1.2)	24 (3.1)	0.0004
Stroke	46 (0.8)	12 (1.3)	6 (1.4)	28 (3.6)	<0.0001
Clinical bleeding requiring transfusion	100 (1.7)	46 (5.1)	18 (4.2)	81 (10.5)	<0.0001

Data are provided as number (percentage) or median (interquartile range range). AKI indicates acute kidney injury; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CVD, cardiovascular disease; ICU, intensive care unit; MACE, major adverse cardiac event; MI, myocardial infarction; NT-proBNP, N-terminal pro–brain natriuretic peptide; and RRT, renal replacement therapy.

*Other includes Asian, American Indian, Native Hawaiin or Pacific Islander.

†Biomarkers were not available in the full study sample.

AKI categories, with the exception of IL-6, which was highest at baseline and peak in the AKI stage 3 group (Table 2).

Primary and Secondary Outcomes

In unadjusted analyses, a stepwise increase in mortality was seen with increasingly higher stages of AKI (31.1%, 38.6%, and 48.9% in AKI stages 1, 2, and 3, respectively, versus 10.2% in those without AKI ; log-rank $P<0.0001$; Table 2). Similar graded associations were seen between higher AKI stages and the in-hospital MACEs as well as complications of cardiac arrest, intensive care unit admission, mechanical ventilation, venous thromboembolism, and clinical bleeding requiring transfusion ($P<0.0001$ for each; Table 2). With multivariate adjustment, the association between AKI and mortality remained significant across AKI stages (AKI stage 1: HR, 1.72 [95% CI, 1.46–2.03]; AKI stage 2: HR, 1.83 [95% CI, 1.52–2.20]; AKI stage 3, HR, 1.69 [95% CI, 1.44–1.98]; Figure 2), although without the stepwise association by AKI stage seen in the unadjusted data. Similar patterns were seen for the association of AKI with MACEs (adjusted HR, 2.17 [95% CI, 1.74–2.71]; HR, 2.70 [95% CI, 2.07–3.51]; HR, 3.06 [95% CI, 2.52–3.72] for AKI stages 1–3, respectively; Figure 2). No independent association was seen between AKI and thromboembolic complications (Figure 2).

In multivariate analyses stratified by in-hospital complications including shock or cardiac arrest and mechanical ventilation, AKI was significantly associated with in-hospital mortality both among patients with and without these complications (Figure 3). The association of AKI stages with mortality remained significant in sensitivity analyses considering the 2 AKI definitions separately (Figure 3).

DISCUSSION

In a large, national, multicenter registry of US patients hospitalized with COVID-19, we confirm previous findings from smaller and more selected cohorts demonstrating that AKI is associated with increased severity of illness, such as shock and mechanical ventilation, and with in-hospital all-cause mortality. Moreover, this study reports important novel associations between AKI and MACEs in patients with COVID-19, an important finding given

Table 3. Multivariate Logistic Regression Model for In-Hospital AKI

Variable	Odds Ratio (95% CI)
Age, per y	1.03 (1.02–1.03)
Male	1.80 (1.56–2.08)
Black race	1.91 (1.61–2.27)
Hispanic ethnicity	0.93 (0.79–1.10)
Other* race	1.04 (0.49–2.21)
Diabetes mellitus	1.48 (1.28–1.72)
Hypertension	1.65 (1.41–1.93)
Prior CVD	1.14 (0.95–1.37)
In-hospital shock	2.19 (1.73–2.76)
In-hospital MI	1.40 (0.88–2.21)
In-hospital CHF	1.48 (0.84–2.61)
In-hospital cardiac arrest	1.69 (1.26–2.27)
Symptom onset (per day)	1.01 (1.00–1.02)
Mechanical ventilation	3.32 (2.72–4.05)

CHF indicates congestive heart failure; CVD, cardiovascular disease; and MI, myocardial infarction.

*Other includes Asian, American Indian, Native Hawaiin or Pacific Islander.

emerging data demonstrating cardiac complications in COVID-19 patients and their contribution to mortality.[14,15,17,27–31] Furthermore, we provide additional novel mechanistic insights from analyses that show that patients with kidney disease, whether acute or chronic, have a significantly more adverse biomarker profile including higher levels of inflammatory and cardiac biomarkers. Finally, the symptom profile differed among patients with CKD or ESKD on presentation (as compared with no CKD), with a higher proportion reporting confusion. Patients with AKI also reported symptoms of confusion more often, whereas constitutional symptoms, headache, anosmia, myalgias, nasal congestion, sore throat, and nausea were less common compared with patients without AKI.

CKD was associated with mortality and other COVID-19 outcomes in univariate analyses, but not after adjustment for comorbid conditions. This is a surprising finding given prior studies linking CKD with higher mortality in COVID-19.[12,18,28] This difference could be explained by the depth of our data collection and multivariate models, which allowed for more extensive adjustment for covariates. In contrast, AKI was strongly associated with increased mortality in COVID-19 after multivariate adjustment, with results similar whether AKI was diagnosed at admission (definition 1) or later, based on serial creatinine changes (definition 2). Results remained robust both when adjusting for, and stratifying by, in-hospital complications that may cause AKI, such as shock or cardiac arrest and respiratory failure requiring mechanical ventilation. Risk was elevated to a similar extent for mild and more severe AKI stages. The associations observed here of AKI with mortality and MACEs appear generally similar to those reported for AKI in other acute hospital illnesses, recognizing the challenges of posttrial comparisons.[1–4,9–13]

Early reports from Wuhan, China, suggested a relatively low incidence of AKI in hospitalized patients with COVID-19, between 1% and 10%.[14–17] Subsequent studies then reported higher proportions of patients with AKI either present on admission or during the index hospitalization for COVID-19, ranging from 14% to 50%.[18–22,32] In our study, the prevalence of AKI of any stage was 16%. In these prior studies, death rates were increased 2-fold to 5-fold among those with AKI.[18,19] However, assessment of the full impact of AKI on patient outcomes in these studies was limited because of the small cohort sizes, inclusion of few centers, or selected study samples (such as intensive care unit patients only). Our large study that includes multiple US health centers confirms a strong connection between the presence of AKI and mortality in COVID-19.

Several potential mechanisms for AKI in COVID-19 have been proposed.[33,34] In a recent consensus statement, these putative mechanisms were classified as direct (ie, renal specific) and indirect (ie, secondary to systemic processes).[33] One direct mechanism is cellular entry of viral particles via the ACE2 (angiotensin-converting enzyme 2) receptor, which is expressed on renal mesangial cells, podocytes, the parietal epithelium of Bowman's capsule, and the collecting ducts.[35] In a postmortem pathologic study of 26 patients who died with COVID-19, 9 patients demonstrated clinical evidence of renal injury, with histopathologic analysis of the kidney significant for nonspecific lymphocytic infiltrate and direct invasion of renal tubules by SARS-CoV-2 particles.[36] It should be noted, however, that renal cell tropism is a debated topic and has not been confirmed as a mechanism of kidney injury in this population. It has been proposed that in addition to direct cytotoxicity by the virus, there is activation of cluster of differentiation (CD) 68+ macrophages and the complement cascade, and potentially contributions from antiphospholipid antibodies, to mediate tubular damage.[37] SARS-CoV-2 viral particles were identified in renal tubular epithelial cells in 1 autopsy case report of a patient with COVID-19 after open repair of aortic dissection.[38] Several other autopsy series and case reports have identified collapsing glomerulopathy as a renal-specific mechanism of COVID-19 kidney injury.[39–43]

The role of the ACE2 enzyme in direct cellular entry of the SARS-CoV-2 viral particles has led to consideration of the renin-angiotensin-aldosterone system in the pathogenesis of kidney disease in COVID-19. It is hypothesized that renin-angiotensin-aldosterone system activation may also contribute to a higher risk

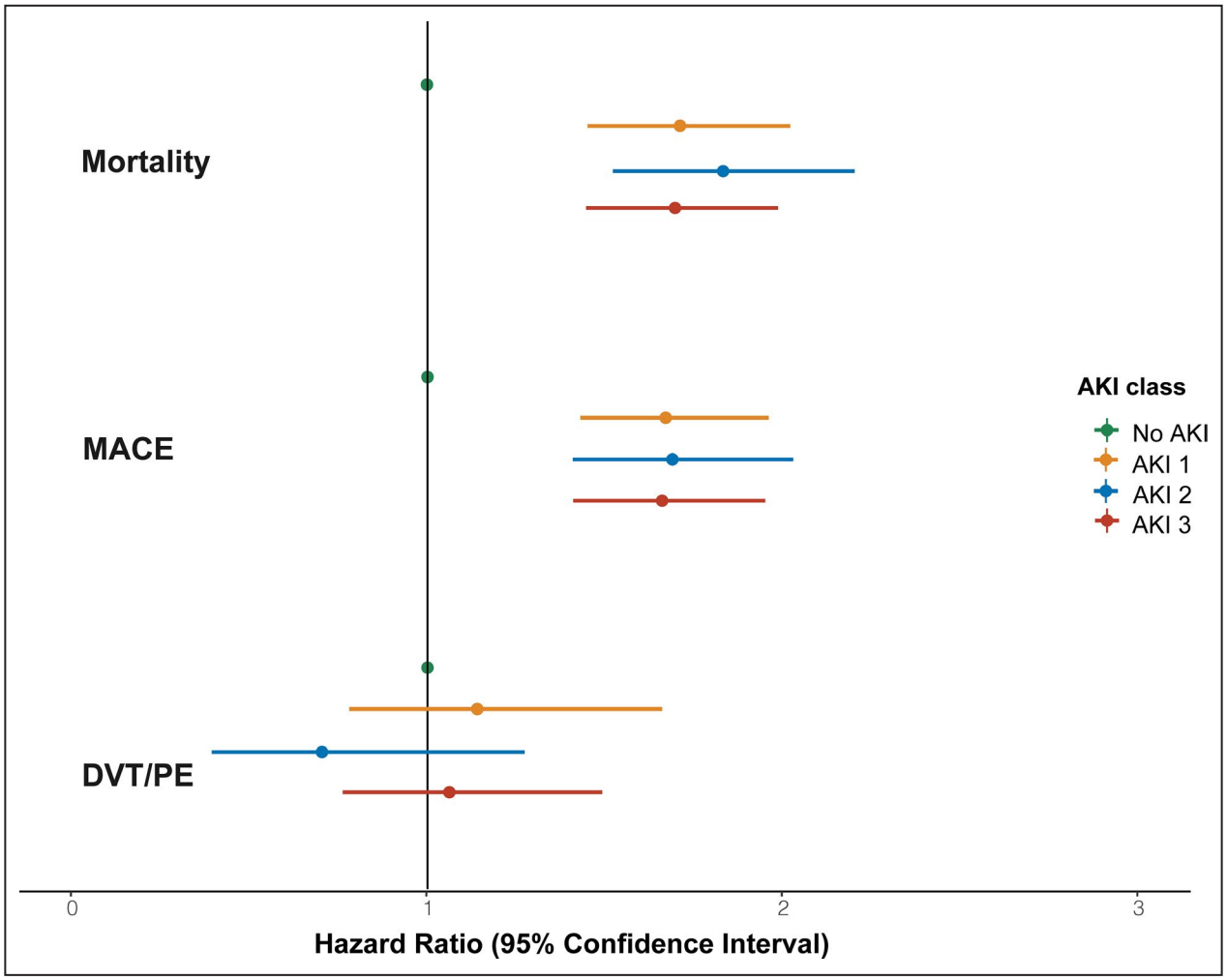

Figure 2. Forest plot of multivariate adjusted primary and key secondary outcomes overall by AKI stage.
Plots represent the hazard ratio with corresponding 95% CI for the corresponding outcome by AKI stage. Green represents no AKI, yellow represents AKI stage 1, blue represents AKI stage 2, and red represents AKI stage 3. Multivariate models included adjustment for age, sex, race/ethnicity, insurance status, smoking, diabetes mellitus, hypertension, and prior cardiovascular disease (coronary artery disease, heart failure, atrial fibrillation, stroke) and chronic kidney disease. Mortality model additionally adjusted for in-hospital shock, myocardial infarction, heart failure, and cardiac arrest. AKI indicates acute kidney injury; AKI 1, AKI stage 1; AKI 2, AKI stage 2; AKI 3, AKI stage 3; DVT, deep vein thrombosis; HR, hazard ratio; MACE, major adverse cardiovascular event; and PE, pulmonary embolism.

of cardiovascular complications in COVID-19,[44] a risk that appears magnified among patients with AKI in our study. The role of ACE2 in the renin-angiotensin-aldosterone system cascade is to degrade angiotensin II, which serves to counter the vasoconstrictive and proinflammatory downstream effects of angiotensin II. It is hypothesized that SARS-CoV-2 downregulates the function of ACE2, leading to the accumulation of angiotensin II and an increase in its vasoactive effects.[45] In addition, the degradation products of angiotensin II have important anti-inflammatory effects that counteract the proinflammatory downstream effects of angiotensin II. These broad pernicious effects of SARS-CoV-2 on ACE2 may thus contribute both to AKI and the higher rates of MACEs among patients with AKI observed in our study.

Early in the COVID-19 pandemic, there was extensive debate about the contribution of renin-angiotensin-aldosterone system inhibition with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to mortality in patients with COVID-19. However, this association has not been shown in recent trials. In a retrospective cohort study by Fosbol and colleagues, among patients with hypertension, prior use of ACEIs or ARBs was not significantly associated with COVID-19 diagnosis, severity, or mortality.[46] Moreover, in the BRACE CORONA trial performed in Brazil, 659 patients taking

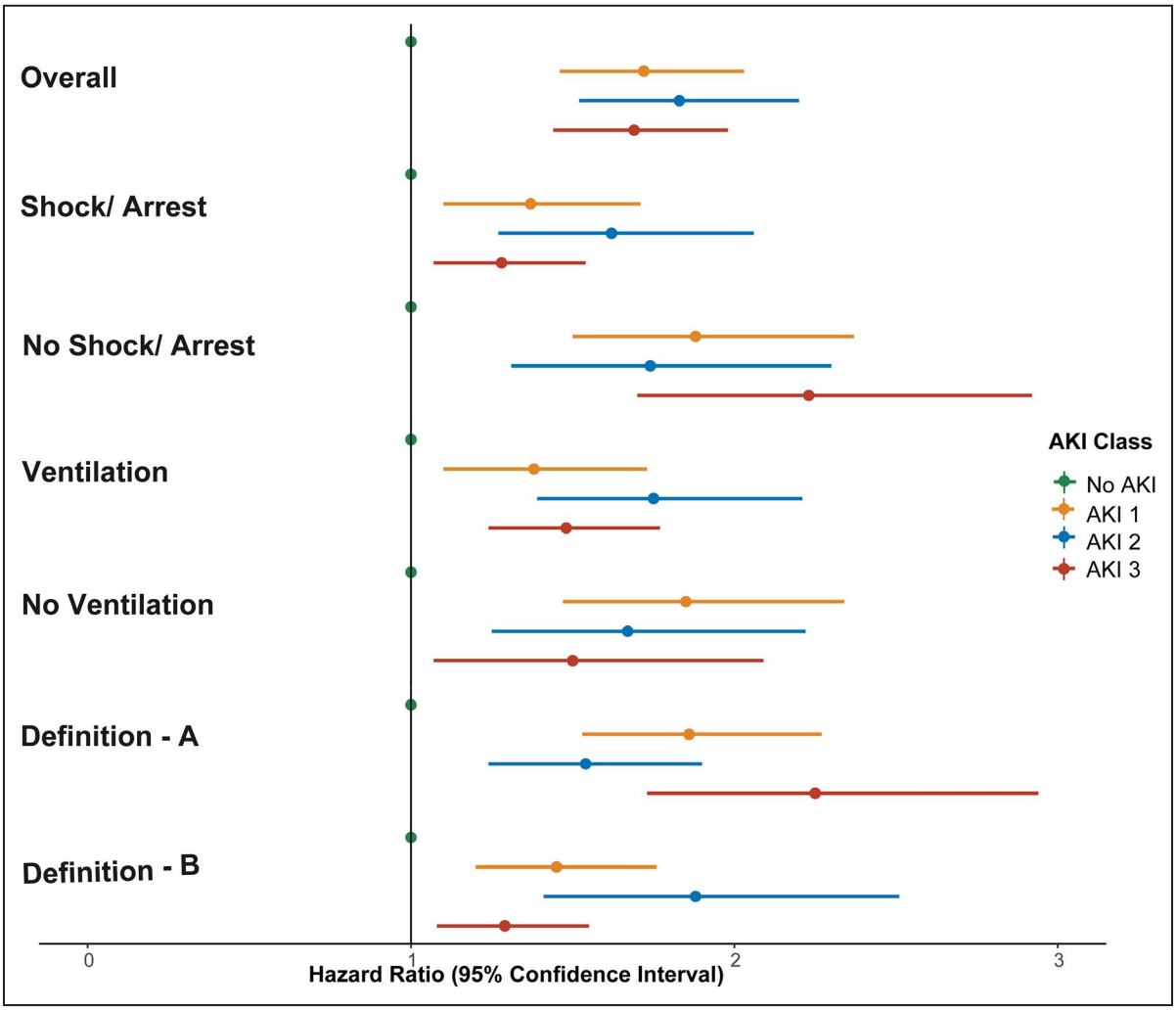

Figure 3. Forest plot of multivariate adjusted associations of AKI with in-hospital mortality, stratified by in-hospital complications or AKI definition.
Plots represent the hazard ratio with corresponding 95% CI for the corresponding outcome by AKI stage. Green represents the "no AKI" group, yellow represents the "stage 1 AKI" group, blue represents the "stage 2 AKI" group, and red represents the "stage 3 AKI" group. Multivariate models included adjustment for age, sex, race/ethnicity, insurance status, smoking, diabetes mellitus, hypertension, and prior cardiovascular disease (coronary artery disease, heart failure, atrial fibrillation, stroke) and chronic kidney disease. Mortality model additionally adjusted for in-hospital shock, myocardial infarction, heart failure, and cardiac arrest except when stratified for these variables. AKI indicates acute kidney injury; AKI 1, AKI stage 1; AKI 2, AKI stage 2; AKI 3, and AKI stage 3.

ACEIs or ARBs before admission for mild to moderate COVID-19 were then randomized to continuation versus discontinuation of ACEIs or ARBs.[47] There was no difference in the number of days alive or out of the hospital between the 2 groups, suggesting that ACEI or ARB continuation was not associated with worse mortality in COVID-19.[47]

Beyond COVID-specific mechanisms, common causes of AKI in hospitalized patients appear to play a role in the development of AKI in patients with COVID-19 and may also contribute to MACEs and death. These indirect mechanisms include hemodynamic instability and shock resulting in acute tubular necrosis; nephrotoxic medications resulting in acute interstitial nephritis; and right ventricular failure and elevated positive end-expiratory pressure levels in patients on mechanical ventilation exacerbating cardiorenal syndrome.[33] Finally, it is possible that renal contraindications to COVID-19 therapies, such as remdesivir, may contribute to worse outcomes, as patients with advanced kidney disease less commonly receive this beneficial therapy.

Our study has several limitations. First, the process of data abstraction into the registry and the lack of prior creatinine measurements may have led to misclassification of patients with CKD as having AKI. The low use of ACEIs/ARBs in the CKD subgroup supports some degree of misclassification of

this definition. This could contribute to the lack of significant association between CKD and adverse outcomes seen in our study. We also did not collect data on the presence of proteinuria, hematuria, or urine sediment analysis, which may have identified patients with earlier stages of renal dysfunction and provided additional information regarding mechanism of AKI in this population. Finally, AKI in patients with COVID-19 may be both an outcome of critical illness and an exposure that contributes to adverse outcomes. The timing of AKI relative to other in-hospital events was not determined. As such, the absence of clear temporal relationships between the development of AKI and the other in-hospital complications limits our evaluation of AKI as an exposure alone in this population. However, the consistency of the mortality associations in subgroups without major in-hospital complications provides strong support that confounding from major hemodynamic and respiratory complications does not fully explain the association of AKI with adverse outcomes.

Our study has potential clinical implications for hospitalized patients with COVID-19. First, the significant association between AKI and mortality in stratified analyses of patients without major complications suggests that kidney injury is an important marker of future adverse outcomes in COVID-19 and is not merely a manifestation of higher disease acuity. Second, the novel findings regarding MACEs suggest that when AKI is detected, heightened awareness for cardiovascular complications is warranted. Cardiovascular prevention may assume a lower priority in individuals admitted with COVID-19 given the high respiratory morbidity and mortality of this illness. However, cardiovascular complications occur in a substantial minority of patients with COVID-19[28–31,45,48] and occur more frequently in patients with AKI, as seen in our study. Future studies should investigate whether continuation or even initiation of cardiovascular preventive therapies, including statins and antiplatelet therapies, could mitigate cardiac risks in patients with COVID-19 and AKI.

Early recognition of AKI in patients with COVID-19 may provide useful information regarding prognosis, regardless of the mechanism or timing of AKI. In turn, close monitoring for hemodynamic fluctuations, maintaining fluid homeostasis, and avoiding nephrotoxins may help to prevent worsening kidney injury during the hospitalization. Additional study is needed to determine whether specific interventions to optimize hemodynamic performance can prevent AKI or mitigate downstream consequences from AKI in COVID-19.

In summary, our study demonstrates that in a large, diverse population of hospitalized patients with COVID-19, AKI present on admission or developing during the index hospitalization for COVID-19 infection is strongly associated with all-cause mortality and with major adverse cardiac events. Further investigations are needed to clarify the mechanisms of AKI and potential treatments for kidney injury beyond supportive care.

ARTICLE INFORMATION

Received January 19, 2021; accepted April 19, 2021.

Affiliations

Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX (A.R., C.A., N.H., A.R., P.M., S.R.D., S.S.H., J.A.d.L.); Parkland Health and Hospital System, Dallas, TX (A.R., N.H., A.R., S.R.D., J.A.d.L.); Department of Cardiovascular Medicine, University of Kansas, Kansas City, KS (S.R., K.G.); American Heart Association, Dallas, TX (H.M.A., C.R.); Department of Internal Medicine, Beth Israel Deaconess Medical Center, Boston, MA (W.O.); Department of Internal Medicine, Yale School of Medicine, New Haven, CT (R.K.); and Inova Heart and Vascular Institute, Fairfax, VA (C.D.).

Sources of Funding

None.

Disclosures

Christopher DeFilippi, MD, reports consulting income and honorarium from Abbott Diagnostics, FujiRebio, Ortho Diagnostics, Quidel, Roche Diagnostics, and Siemens Healthcare Diagnostics. S. Susan Hedayati, MD, MSc, is supported by the Yin Quan-Yuen Distinguished Professorship in Nephrology at the University of Texas Southwestern Medical Center, Dallas, TX. The remaining authors have no disclosures to report.

REFERENCES

1. Mody P, Wang T, McNamara R, Das S, Li S, Chiswell K, Tsai T, Kumbhani D, Wiviott S, Goyal A, et al. Association of acute kidney injury and chronic kidney disease with processes of care and long-term outcomes in patients with acute myocardial infarction. *Eur Heart J - Qual Care Clin Outcomes*. 2018;4:43–50. DOI: 10.1093/ehjqcco/qcx020.
2. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67. DOI: 10.1016/j.jacc.2003.07.031.
3. Neyra JA, Mescia F, Li X, Adams-Huet B, Yessayan L, Yee J, Toto RD, Moe OW. Impact of acute kidney injury and CKD on adverse outcomes in critically ill septic patients. *Kidney Int Rep*. 2018;3:1344–1353. DOI: 10.1016/j.ekir.2018.07.016.
4. Neyra JA, Li X, Canepa-Escaro F, Adams-Huet B, Toto RD, Yee J, Hedayati SS; Acute Kidney Injury in Critical Illness Study Group. Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. *Crit Care Med*. 2016;44:1891–1900. DOI: 10.1097/CCM.0000000000001835.
5. Zoccali C, Vanholder R, Massy ZA, Ortiz A, Sarafidis P, Dekker FW, Fliser D, Fouque D, Heine GH, Jager KJ, et al.; European Renal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA). The systemic nature of CKD. *Nat Rev Nephrol*. 2017;13:344–358. DOI: 10.1038/nrneph.2017.52.
6. Hernandez-Vasquez A, Azanedo D, Vargas-Fernandez R, Bendezu-Quispe G. Association of comorbidities with pneumonia and death among COVID-19 patients in Mexico: a nationwide cross-sectional study. *J Prev Med Public Health*. 2020;53:211–219. DOI: 10.3961/jpmph.20.186.
7. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. *Int Urol Nephrol*. 2020;52:1193–1194. DOI: 10.1007/s11255-020-02451-9.
8. Martin-Loeches I, Papiol E, Rodríguez A, Diaz E, Zaragoza R, Granada RM, Socias L, Bonastre J, Valverdú M, Pozo JC, et al. Acute kidney injury in critically ill patients affected by influenza A (H1N1) virus infection. *Crit Care*. 2011;15:R66. DOI: 10.1186/cc10046.

9. Bagshaw SM, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, Ellis P, Guzman J, Marshall J, Parrillo JE, et al.; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med*. 2009;35:871–881. DOI: 10.1007/s00134-008-1367-2.
10. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, et al.; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol*. 2007;2:431–439. DOI: 10.2215/CJN.03681106.
11. Neveu H, Kleinknecht K, Brivet F, Loirat P, Landais P. Prognostic factors in acute renal failure due to sepsis: results of a prospective multicentre study. The French study group on acute renal failure. *Nephrol Dial Transplant*. 1996;11:293–299. DOI: 10.1093/oxfordjournals.ndt.a027256.
12. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, Angus DC, Kellum JA; Genetic and Inflammatory Markers of Sepsis (GenIMS) Investigators. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int*. 2010;77:527–535. DOI: 10.1038/ki.2009.502.
13. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, Hunn BH. AKI and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol*. 2017;28:377–387. DOI: 10.1681/ASN.2016010105.
14. Guan W-J, Ni Z-Y, Hu YU, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720. DOI: 10.1056/NEJMoa2002032.
15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu YI, Zhang LI, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. DOI: 10.1016/S0140-6736(20)30183-5.
16. Wang D, Hu BO, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069. DOI: 10.1001/jama.2020.1585.
17. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513. DOI: 10.1016/S0140-6736(20)30211-7.
18. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020;97:829–838. DOI: 10.1016/j.kint.2020.03.005.
19. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium, Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98:209–218. DOI: 10.1016/j.kint.2020.05.006.
20. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: our experience from Seattle. *Am J Kidney Dis*. 2020;76:4–6. DOI: 10.1053/j.ajkd.2020.04.001.
21. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, Sutherland A, Puri S, Srivastava A, Leonberg-Yoo A, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. *J Am Soc Nephrol*. 2021;32:161–176. DOI: 10.1681/ASN.2020060897.
22. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, Paranjpe I, Somani S, Richter F, Miotto R, et al. AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol*. 2021;32:151–160. DOI: 10.1681/ASN.2020050615.
23. Alger HM, Rutan C, Williams JH, Walchok JG, Bolles M, Hall JL, Bradley SM, Elkind MSV, Rodriguez F, Wang TY, et al. American Heart Association COVID-19 CVD Registry powered by Get With The Guidelines. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006967. DOI: 10.1161/CIRCOUTCOMES.120.006967.
24. Rodriguez F, Solomon N, de Lemos JA, Das SR, Morrow DA, Bradley SM, Elkind MSV, Williams JH IV, Holmes D, Matsouaka RA, et al. Racial and ethnic differences in presentation and outcomes for patients hospitalized with COVID-19: findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry. *Circulation*. 2020. DOI: 10.1161/CIRCULATIONAHA.120.052278.
25. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, et al. Association of body mass index and age with morbidity and mortality in patients hospitalized with COVID-19: results from the American Heart Association COVID-19 Cardiovascular Disease Registry. *Circulation*. 2021;143:135–144. DOI: 10.1161/CIRCULATIONAHA.120.051936.
26. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guidelines for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
27. Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Lucca B, Cortinovis R, et al. A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection. *Kidney Int*. 2020;98:20–26. DOI: 10.1016/j.kint.2020.04.030.
28. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. DOI: 10.1016/S0140-6736(20)30566-3.
29. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol*. 2020;76:533–546. DOI: 10.1016/j.jacc.2020.06.007.
30. Shi S, Qin MU, Shen BO, Cai Y, Liu T, Yang F, Gong W, Liu XU, Liang J, Zhao Q, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5:802–810. DOI: 10.1001/jamacardio.2020.0950.
31. Zheng Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260. DOI: 10.1038/s41569-020-0360-5.
32. Ng JH, Hirsch JS, Hazzan A, Wanchoo R, Shah HH, Malieckal DA, Ross DW, Sharma P, Sakhiya V, Fishbane S, et al. Northwell Nephrology COVID-19 Research Consortium. Outcomes among patients hospitalized with COVID-19 and acute kidney injury. *Am J Kidney Dis*. 2021;77:204–215. DOI: 10.1053/j.ajkd.2020.09.002.
33. Nadim MK, Forni LG, Mehta RL, Conner MJ Jr, Liu KD, Ostermann M, Rimmele T, Zarbock A, Bell S, Bihorac A, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol*. 2020;16:747–764. DOI: 10.1038/s41581-020-00356-5.
34. Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L. Acute kidney injury in critically ill patients with COVID-19. *Intensive Care Med*. 2020;46:1339–1348. DOI: 10.1007/s00134-020-06153-9.
35. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. *Nat Rev Nephrol*. 2020;16:308–310. DOI: 10.1038/s41581-020-0284-7.
36. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631–637. DOI: 10.1002/path.1570.
37. Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, Yi F, Yang H-C, Fogo AB, Nie X, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98:219–227. DOI: 10.1016/j.kint.2020.04.003.
38. Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, Wang C, Liu L, Liu Y, Liu Y, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Preprint from medRxiv. 2020. DOI: 10.1101/2020.03.04.20031120.
39. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural evidence for direct renal infection with SARS-CoV-2. *J Am Soc Nephrol*. 2020;31:1683–1687. DOI: 10.1681/ASN.2020040432.
40. Peleg Y, Kudose S, D'Agati V, Siddall E, Ahmad S, Nickolas T, Kisselev S, Gharavi A, Canetta P. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. *Kidney Int Rep*. 2020;5:940–945. DOI: 10.1016/j.ekir.2020.04.017.
41. Larsen CP, Bourne TD, Wilson JD, Saqqa O, Sharshir MA. Collapsing glomerulopathy in a patient with COVID-19. *Kidney Int Rep*. 2020;5(6):935–939. DOI: 10.1016/j.ekir.2020.04.002.
42. Kissling S, Rotman S, Gerber C, Halfon M, Lemoth F, Comte D, Lhopitallier L, Sadallah S, Fakhouri F. Collapsing glomerulopathy in a COVID-19 patient. *Kidney Int*. 2020;93:228–231. DOI: 10.1016/j.kint.2020.04.006.

43. Nasr SH, Kopp JB. COVID-19-associated collapsing glomerulopathy: an emerging entity. *Kidney Int Rep*. 2020;5:759–761. DOI: 10.1016/j.ekir.2020.04.030.
44. Hanff TC, Harhay O, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system? A call for epidemiologic investigations. *Clin Infect Dis*. 2020;71:870–874. DOI: 10.1093/cid/ciaa329.
45. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation*. 2020;141:1903–1914. DOI: 10.1161/CIRCULATIONAHA.120.047349.
46. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, Schou M, Phelps M, Gislason GH, Gerds TA, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA*. 2020;324:168–177. DOI: 10.1001/jama.2020.11301.
47. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, dos Santos TM, Mazza L, Feldman A, D'Andréa Saba Arruda G, de Albuquerque DC, Camiletti AS, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. 2021;325:254–264. DOI: 10.1001/jama.2020.25864.
48. Hendren NS, Grodin JL, Drazner MH. Unique patterns of cardiovascular involvement in Coronavirus Disease-2019. *J Card Fail*. 2020;26:466–469. DOI: 10.1016/j.cardfail.2020.05.006.