Acute and Chronic Kidney Disease and Cardiovascular Mortality After Major Surgery

Tezcan Ozrazgat-Baslanti, PhD, Paul Thottakkara, MS Eng,* Matthew Huber, BS,* Kent Berg, MD, MBA,* Nikolaus Gravenstein, MD,* Patrick Tighe, MD, MS,* Gloria Lipori, MBA,† Mark S. Segal, MD, PhD,‡ Charles Hobson, MD, MHA,§¶ and Azra Bihorac, MD, MS*‡*

Objective: The aim of the study was to determine the long-term cardiovascular-specific mortality in patients with acute kidney injury (AKI) or chronic kidney disease (CKD) after major surgery.

Background: In surgical patients, pre-existing CKD and postoperative AKI are associated with increases in all-cause mortality.

Methods: In a single-center cohort of 51,457 adult surgical patients undergoing major inpatient surgery, long-term cardiovascular-specific mortality was modeled using a multivariable subdistributional hazards model while treating any other cause of death as a competing risk and accounting for the progression to end-stage renal disease (ESRD) after discharge. Pre-existing CKD and ESRD, and postoperative AKI were the main independent predictors.

Results: Before the admission, 4% and 8% of the cohort had pre-existing ESRD and CKD not requiring renal replacement therapy, respectively. During hospitalization, 39% developed AKI. At 10-year follow-up, adjusted cardiovascular-specific mortality estimates were 6%, 11%, 12%, 19%, and 27% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, AKI with CKD, and ESRD, respectively ($P < 0.001$). This association remained after excluding 916 patients who progressed to ESRD after discharge, although it was significantly amplified among them. Compared with patients having no kidney disease, adjusted hazard ratios for cardiovascular mortality were significantly higher among patients with kidney disease, ranging from 1.95 (95% confidence interval, 1.80–2.11) for patients with de novo AKI to 5.70 (95% confidence interval, 5.00–6.49) for patients with pre-existing ESRD.

Conclusions: Both AKI and CKD were associated with higher long-term cardiovascular-specific mortality compared with patients having no kidney disease.

Keywords: acute kidney injury, cardiovascular-specific mortality, cause of death, chronic kidney disease, competing risk, end-stage renal disease progression, survival

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Acute kidney injury (AKI) is independently associated with the development of chronic kidney disease (CKD), end-stage renal disease (ESRD), and increased all-cause mortality.[1–8] The severity of the renal insult and the development of multiple AKI episodes increase the risk of occurrence of these outcomes.[5,7,8]

All severity stages of CKD, from mild disease to the dialysis-dependent ESRD, are associated with an increase in cardiovascular risk and mortality.[9] Furthermore, both a decline in estimated glomerular filtration rate (eGFR) and albuminuria are important determinants of longevity in the general population.[10] Recent studies suggested AKI as a risk factor for cardiovascular disease either through progression to CKD or through independent mechanisms.[11,12] Patients with AKI had increased risk for subsequent congestive heart failure, coronary artery disease, and de novo stroke, regardless of progression to CKD.[13–15] Patients hospitalized for myocardial infarctions whose stay was complicated by the AKI were more likely to have a subsequent admission for an adverse cardiac event compared with those patients who did not develop AKI.[11]

In surgical patients, CKD is an important risk factor for 30-day mortality,[16] and postoperative AKI is associated with increase in all-cause mortality.[17–20] Previous studies in surgical patients were focused on all-cause mortality rather than cardiovascular causes, with assumption that progression to ESRD is the underlying mechanism for observed mortality increase.[12] Furthermore, since patients with kidney disease often have a decrease in hemoglobin levels, and chronic and acute anemia in the perioperative setting increases the risk for adverse outcomes,[21] it is important to delineate whether their effects are interrelated.[22]

In a large, single-center cohort of surgical patients, we examined the long-term cardiovascular-specific mortality in patients with either acute or CKD while adjusting for demographic characteristics, comorbidity burden, operative variables, admission hemoglobin levels, progression to ESRD, and other competing causes of death.

METHODS

Data Source and Participants

Using the University of Florida Integrated Data Repository we have previously assembled a single-center cohort of patients aged above or equal to 18 years admitted to the hospital for longer than

From the *Department of Anesthesiology, University of Florida, Gainesville, FL; †Chief Data Officer, University of Florida Health and Science Center, Gainesville, FL; ‡Department of Medicine, University of Florida, Gainesville, FL; §Department of Surgery, Malcom Randall VA Medical Center, Gainesville, FL; and ¶Department of Health Services Research, Management, and Policy, University of Florida, Gainesville, FL.

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The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the United States government.

Reprints: Azra Bihorac, MD, MS, Department of Anesthesiology, P.O. Box 100254, Gainesville, FL 32610-0254. E-mail: abihorac@anest.ufl.edu.

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24 hours after any type of inpatient operative procedure between January 1, 2000 and November 30, 2010.[17] For patients with multiple surgeries, we chose the first procedure. After excluding patients with missing serum creatinine (n = 6636), the final cohort consisted of 51,457 patients. The study was approved by the Institutional Review Board and Privacy Office of the University of Florida.

Deaths

The main outcome of the study was the cardiovascular-specific death, with any other cause of death being treated as a competing risk. For the secondary analysis, the cancer-specific death was treated as the main cause of death in a competing risk model. The date of death was determined using hospital records, the Social Security Death Index (SSDI), and Florida Bureau of Vital Statistics. The survival time was calculated from the admission date to the date of death from any cause or the date at which the patient was last known alive. We used full name, birth date, and social security number to search the SSDI in July 2014 to assess survival through January 31, 2014 that was also the date of data censoring for patients who were last known to be alive. Primary cause of death was obtained from death certificates from the Florida Bureau of Vital Statistics using a matching algorithm that utilized full name, date of birth, and date of death. About 10% of nonsurvivors did not have matching cause of death, likely reflecting death records from other states. Since November 2011, Social Security Administration has imposed changes mandating that states were no longer permitted to share data on deaths in SSDI.[23] To determine whether this change affected our analyses, we performed sensitivity analysis by censoring all patients known to be alive or who had died after October 31, 2011 on that day and by excluding records without cause of death from analysis. Using the International Classification of Diseases, Tenth Revision (ICD-10) for the primary cause of death on the death certificate, we classified deaths into cardiovascular-specific (ICD-10 codes I00-I99, Q20-Q28, E10-E14, N00-N08, N10-N16, N17-N19), cancer-specific (codes C00-C97), and all other causes. We included diabetes and kidney disease into the expanded cardiovascular-specific category to capture deaths related to CKD, but traditionally not classified as cardiovascular as previously reported.[9] For sensitivity analysis, we used alternative approach reported for the general population.[24,25]

Definition of Kidney Disease and Covariates

The main covariate of interest was the occurrence of AKI or CKD during the index hospitalization. For all patients, we calculated a reference eGFR using standardized reference serum creatinine, sex, race, and age.[26] For the reference creatinine we used the minimum of values available within 6 months before admission, or the minimum and mean of the creatinine values available within 7 days before admission (used for sensitivity analyses).[27] Patients with CKD and ESRD before admission were identified using the validated combination of ICD-9-CM codes.[28] Patients with CKD were stratified using reference eGFR without criteria for albuminuria into mild to moderate (eGFR ≥ 30 mL/min/1.73 m^2) and severe CKD (eGFR < 30 mL/min/1.73 m^2) according to guidelines.[29] We defined AKI using the ''Kidney Disease: Improving Global Outcomes'' (KDIGO) criteria as at least a 50% or 0.3 mg/dL increase in serum creatinine relative to the reference value and stratified AKI severity based on the maximum change in serum creatinine during hospitalization.[30] Progression to ESRD after discharge was determined by linking records of discharged patients with the United States Renal Data System (USRDS) database using their matching algorithm. Time to ESRD was calculated from the discharge date to the date of the first ESRD Service.[31] Patients whose primary surgery was renal transplant were excluded from the analysis. The presence of underlying comorbidities was identified by validated ICD-9-CM codes and using the Charlson-Deyo comorbidity index.[32] We defined postoperative complications using previously described criteria.[18] We classified all surgeries as cardiothoracic, noncardiac general and vascular, neurologic, specialty (orthopedic, gynecological, otorhinolaryngology, urology, and plastic), and other surgery (burn, transplantation, and trauma). We categorized admission hemoglobin values into missing, less than 8 g/dL, 8 to 9.9 g/dL, 10 to 11.9 g/dL, and at least 12 g/dL. The thresholds were developed after constructing spline function of hemoglobin values and the risk of mortality in univariate analysis, and are similar to previously used values in patients with kidney disease.[22]

Statistical Analysis

The analytical plan followed the ''Strengthening the Reporting of Observational Studies in Epidemiology'' recommendations.[33] Kaplan-Meier estimates were used to calculate cumulative survival probabilities for all-cause mortality. We used the proportional subdistribution hazards regression analyses to model cardiovascular and cancer-specific mortality while treating any other cause of death as a competing risk; and progression to ESRD while treating death from any cause before ESRD as a competing risk.[34] The application of the regression modeling directly on a cumulative incidence function allows the best estimation of the effect of covariates in the model.[35] In addition to the occurrence of kidney disease, each model was adjusted for preoperative demographic covariates, Charlson comorbidity index, emergent surgery status, surgery type, and admission day hemoglobin level. Adjusted hazards ratios with 95% confidence intervals (95% CIs) were reported for each covariate in the model. We plotted unadjusted and adjusted model-based cumulative incidence functions of the cardiovascular and cancer-specific mortality and ESRD progression by kidney disease, and severity stages for the entire cohort and for patients grouped by sex and age, and by surgery type. We used independent validation datasets created with a bootstrap cross-validation method for internal validation and to assess prediction accuracy of the models. The models were trained on 100 bootstrap samples that were drawn with replacement of 60% of the original data and were validated in the bootstrap samples that did not contain any observations from the training datasets. We compared the discriminative power of competing risk models between training and cross-validation datasets using the adaptation of Harrell concordance probability to the competing risk setting by calculating the C-index, with 95% CI for both training and validation datasets.[36] Sensitivity analyses were performed by running the competing risk models after censoring all patients who were last known to be alive or who had died after October 31, 2011, using alternative classification for cardiovascular cause of death, excluding patients with unknown cause of death, using different methods for missing hemoglobin values and reference serum creatinine, by including individual comorbidities instead of Charlson-Deyo comorbidity index, and by adding total number of postoperative complications as a covariate. All significance tests were 2-sided, with a P value less than 0.05 considered statistically significant. Statistical analyses were performed with R 3.2.0 (cmprsk and pec packages)[37] and SAS (v.9.3, Cary, NC).

RESULTS

Baseline Characteristics

Overall 44% of the 51,457 surgical patients had evidence of either chronic or acute kidney disease during hospitalization (Table 1 and SDC Tables 1 and 2, http://links.lww.com/SLA/A938). At the time of admission, 4% and 8% of the cohort had documented history of ESRD and CKD not requiring renal replacement therapy,

TABLE 1. Clinical Characteristics for All Patients Stratified by Kidney Disease

Variables	No Known Kidney Disease (n = 28,644, 56%)	Acute Kidney Injury Without Chronic Kidney Disease (n = 16,854, 33%)	Acute Kidney Injury With Chronic Kidney Disease (n = 3171, 6%)	Chronic Kidney Disease Without Acute Kidney Injury (n = 853, 2%)	End-Stage Renal Disease (n = 1935, 4%)
Age (y), mean (SD)	53 (17)	57 (17)*	62 (15)*	65 (16)*	53 (15)
Age ≥65 y, n (%)	7864 (27)	6326 (38)*	1491 (47)*	493 (58)*	481 (25)
Female sex, n (%)	15012 (52)	7658 (45)*	11224 (39)*	415 (49)	811 (42)*
African-American ethnicity, n (%)	3345 (12)	1859 (11)	591 (19)*	118 (14)	671 (35)*
Rural area residency, n (%)	9277 (32)	5311 (32)	1008 (32)	274 (32)	534 (28)*
Distance from residing neighborhood to hospital, km, median (25th, 75th)	52 (23, 117)	56 (27, 120)*	57 (27, 120)	49 (23, 118)	76 (28, 171)
Population living in poverty in residing neighborhood, % (SD)	14.9 (8.4)	14.6 (8.1)*	15.0 (8.4)	14.7 (8.1)	15.4 (8.6)*
Primary insurance, n (%)					
Medicare	9310 (33)	7173 (43)*	1897 (60)*	560 (66)*	1280 (66)*
Medicaid	3835 (13)	2233 (13)	307 (10)*	74 (9)*	133 (7)*
Private	12972 (45)	6343 (38)*	879 (28)*	204 (24)*	510 (26)*
Uninsured	2527 (9)	1105 (7)*	88 (3)*	15 (2)*	12 (1)*
Emergent surgery, n (%)	10543 (37)	9545 (57)*	1909 (60)*	318 (37)	1276 (66)*
Weekend admission, n (%)	3175 (11)	2940 (17)*	533 (17)*	89 (10)	378 (20)*
Charlson-Deyo comorbidity score, n (%)					
0	13297 (46)	4782 (28)*	267 (8)*	141 (17)*	5 (0.3)*
1	5420 (19)	3932 (23)*	386 (12)*	107 (13)*	8 (0.4)*
2	4898 (17)	3534 (21)*	688 (22)*	185 (22)*	643 (33)*
≥3	5029 (18)	4606 (27)*	1830 (58)*	420 (49)*	1279 (66)*
Comorbidities, n (%)					
Hypertension	10953 (38)	7386 (44)*	1781 (56)*	550 (64)*	1184 (61)*
Cancer	5901 (21)	3553 (21)	455 (14)*	171 (20)	72 (4)*
Diabetes	3956 (14)	2863 (17)*	968 (31)*	268 (31)*	728 (38)*
Chronic Pulmonary disease	3962 (14)	3247 (19)*	694 (22)*	165 (19)*	235 (12)
Peripheral vascular disease	2427 (8)	2558 (15)*	696 (22)*	168 (20)*	218 (11)*
Cerebrovascular disease	1786 (6)	1945 (12)*	315 (10)*	76 (9)*	119 (6)
Congestive heart failure	984 (3)	1931 (11)*	787 (25)*	128 (15)*	274 (14)*
Myocardial infarction	1276 (4)	1451 (9)*	380 (12)*	99 (12)*	170 (9)*
Liver disease	871 (3)	1209 (7)*	312 (10)*	29 (3)	104 (5)*
Surgery type, n (%)					
Cardiothoracic surgery	2354 (8)	3329 (20)*	842 (27)*	114 (13)*	251 (13)*
Neurologic surgery	5667 (20)	2340 (14)*	240 (8)*	112 (13)*	63 (3)*
Noncardiac general surgery	5901 (22)	3799 (23)*	646 (20)	196 (23)	439 (23)
Specialty surgeries†	10733 (37)	3469 (21)*	613 (19)*	350 (41)	120 (6)*
Other surgeries ‡	3989 (14)	3917 (23)*	830 (26)*	81 (10)*	1062 (55)*
Admission hemoglobin, g/dL, n (%)					
Missing	10371 (36)	3268 (19)*	564 (18)*	291 (34)	374 (19)*
<10	3201 (11)	3320 (20)*	813 (26)*	146 (17)*	355 (18)*
(10, 12)	5912 (21)	4438 (26)*	962 (30)*	238 (28)*	589 (30)*
≥12	9160 (32)	5828 (35)	832 (26)*	178 (21)*	617 (32)
Chronic kidney disease, n (%)					
Mild to moderate (eGFR ≥ 30 mL/min/1.73 m^2)	NA	NA	2022 (64)	787 (92)	NA
Severe (eGFR < 30 mL/min/1.73 m^2)	NA	NA	1149 (36)§	66 (8)	NA

*P value less than 0.05 for comparison with respect to no known kidney disease group using Bonferroni adjustment.
†Specialty surgeries include orthopedic, gynecological, ear-nose-throat, urology, and plastic surgeries.
‡Other surgeries include trauma, burn, and transplant surgeries.
§P value less than 0.05 for comparison with respect to mild to moderate chronic kidney disease group.
NA indicates not applicable; SD, standard deviation.

respectively. Among patients with CKD, 30% (1215/4024) presented with severe disease (eGFR <30 mL/min/1.73 m^2). During hospitalization, 39% of patients developed AKI and the majority of them did not have a history of CKD before admission. Patients with severe CKD were more likely to develop AKI compared with those having mild to moderate disease ($P < 0.001$). African-American ethnicity was more common among patients with CKD and ESRD before admission. Patients with AKI or CKD were more likely to be older men and to have multiple comorbidities compared with patients having no kidney disease. Emergent surgery was more common among patients with AKI and those who had ESRD before admission.

All-cause Mortality, Cause of Death, and Progression to End-stage Renal Disease

The median follow-up time for the cohort was 7 years (interquartile range [IQR] 5–10 y). Overall survival rates for all-cause mortality among patients with any type of kidney disease were

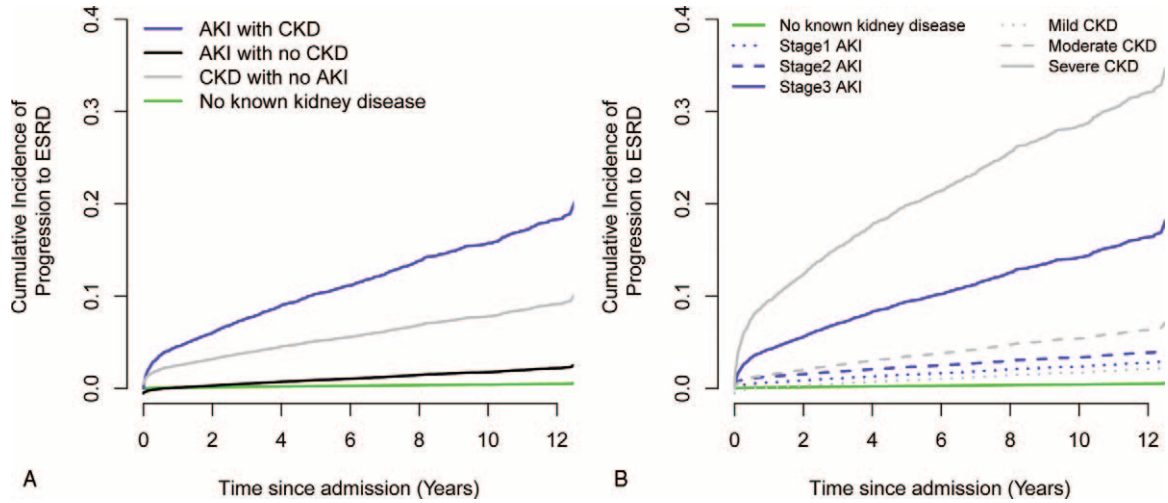

FIGURE 1. Adjusted cumulative incidence curves for progression to end-stage renal disease (A) by kidney disease status and (B) by severity stages (adjusted for age, sex, ethnicity, Charlson comorbidity index, emergent surgery status, surgery type, and admission day hemoglobin level as described in the ''Methods'' section). All groups with acute or chronic kidney disease have significantly higher hazards ratios compared with no known kidney disease group with *P* value less than 0.001.

significantly lower compared with patients with no kidney disease ($P < 0.0001$). At 10-year follow-up, cumulative survival probability for the group with no kidney disease was 75%, whereas it ranged between 39% and 55% for patients with kidney disease (SDC Fig. 1, http://links.lww.com/SLA/A938). The top 2 causes of all deaths were cancer (5051/15247, 33%) and cardiovascular diseases (4269/15247, 28%). Cardiovascular disease accounted for more deaths among patients with any type of kidney disease compared with 18% among patients with no kidney disease ($P < 0.0001$), ranging from 29% for patients with AKI and no CKD, 35% for patients with CKD but no AKI, 45% for those with CKD and AKI during admission, and 55% for ESRD patients. In contrast, cancer accounted for fewer deaths among patients with kidney disease compared with those without (SDC Fig. 1, http://links.lww.com/SLA/A938).

Among patients without prior history of ESRD who were discharged alive, 916 (1.9%) progressed to ESRD after discharge: 0.3% among patients with no known kidney disease, 2.0% among patients with de novo AKI, 7.4% among patients with CKD and no AKI during admission, and 18.9% among CKD patients who developed AKI after surgery. When death from any cause was treated as a competing risk, adjusted ESRD progression estimates at 10-year follow-up were 0.4%, 2.3%, 7.3%, and 15.7% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, and AKI with CKD, respectively ($P < 0.001$ compared with no kidney disease group; Fig. 1A). The rates of progression to ESRD were increased with increasing severity of CKD and AKI (Fig. 1B).

Cardiovascular-specific Mortality and Competing Risk Models

Both unadjusted and adjusted cumulative cardiovascular-specific mortality rates were significantly higher among patients with any type of kidney disease compared with those without (Fig. 2 and SDC Fig. 2, http://links.lww.com/SLA/A938). This association remained after excluding the patients who progressed to ESRD (SDC Fig. 3A, http://links.lww.com/SLA/A938). At 10-year follow-up, adjusted cardiovascular-specific mortality estimates were 6%, 11%, 12%, 19%, and 27% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, AKI with CKD, and ESRD, respectively ($P < 0.001$ compared with no kidney disease group). Among small proportion of cohort who progressed to ESRD, cardiovascular-specific mortality rates were amplified in all groups and comparable with the rates for patients with ESRD before surgery (SDC Fig. 3B, http://links.lww.com/SLA/A938). In contrast, at 10-year follow-up, adjusted cancer-specific mortality rates were lower among patients with kidney disease, and ranged from 13%, 13%, 7%, 5%, and 2% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, AKI with CKD, and ESRD, respectively (SDC Fig. 4, http://links.lww.com/SLA/A938). At 10 years, cumulative incidence rates for progression to ESRD and cardiovascular

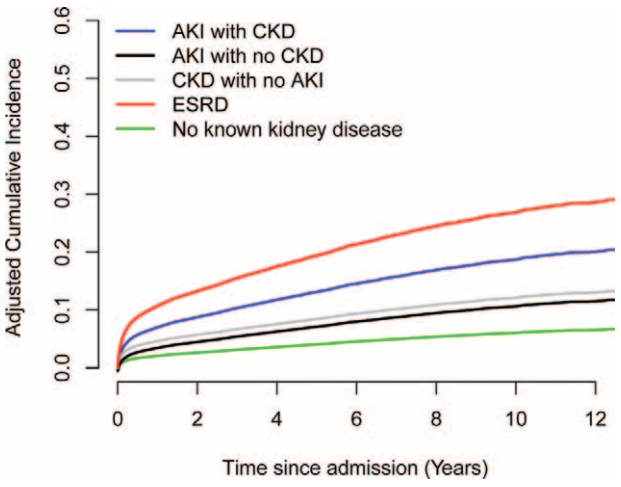

FIGURE 2. Adjusted cumulative incidence curves for cardiovascular-specific mortality by kidney disease status (adjusted for age, sex, ethnicity, Charlson comorbidity index, emergent surgery status, surgery type, and admission day hemoglobin level as described in the ''Methods'' section). All groups with acute or chronic kidney disease have significantly higher hazards ratios compared to no known kidney disease group with *P* value less than 0.001.

TABLE 2. Adjusted 10-year Cumulative Incidence Rates Using Multivariable Subdistributional Hazards Models

Group	Patients, Number*	Cardiovascular-specific Mortality (%)	Cancer-specific Mortality (%)	Progression to ESRD (%)
No known kidney disease	28644	6	13	0.4
Acute kidney injury without chronic kidney disease	16854	11	13	2.3
Acute kidney injury with chronic kidney disease	3171	19	5	15.7
Chronic kidney disease without acute kidney injury	853	12	7	7.3
End stage renal disease	1935	27	2	

*Number of patients for the analysis of progression to ESRD were 28490, 15495, 2445, and 810 for no known kidney disease, AKI with no CKD, AKI with CKD, and CKD with no AKI groups, respectively, as patients with prior history of ESRD, renal transplant as primary surgery, and inhospital mortality were excluded.

mortality among patients with CKD and AKI exceeded the cumulative incidence rate for cancer mortality (Table 2).

The unadjusted and adjusted cardiovascular-specific mortality rates associated with kidney disease remained increased when cohort was stratified by age, sex, and surgery type (Fig. 3 and SDC Figs. 5 and 6, http://links.lww.com/SLA/A938). Even younger, premenopausal women with kidney disease had increase in cardiovascular mortality (at 10-y follow-up, adjusted cardiovascular-specific mortality estimates were 1%, 5%, 8%, 10%, and 10% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, AKI with CKD, and ESRD, respectively; $P < 0.001$). The risk for cardiovascular-specific mortality was amplified by age for both women and men. At 10-year follow-up, among patients aged at least 65 years, adjusted cardiovascular-specific mortality estimates for women and men were 11% to 13%, 19% to 20%, 17% to 20%, 30% to 32%, and 42% to 50% for patients with no kidney disease, AKI with no CKD, CKD with no AKI, AKI with CKD, and ESRD, respectively ($P < 0.001$ compared with no kidney disease group).

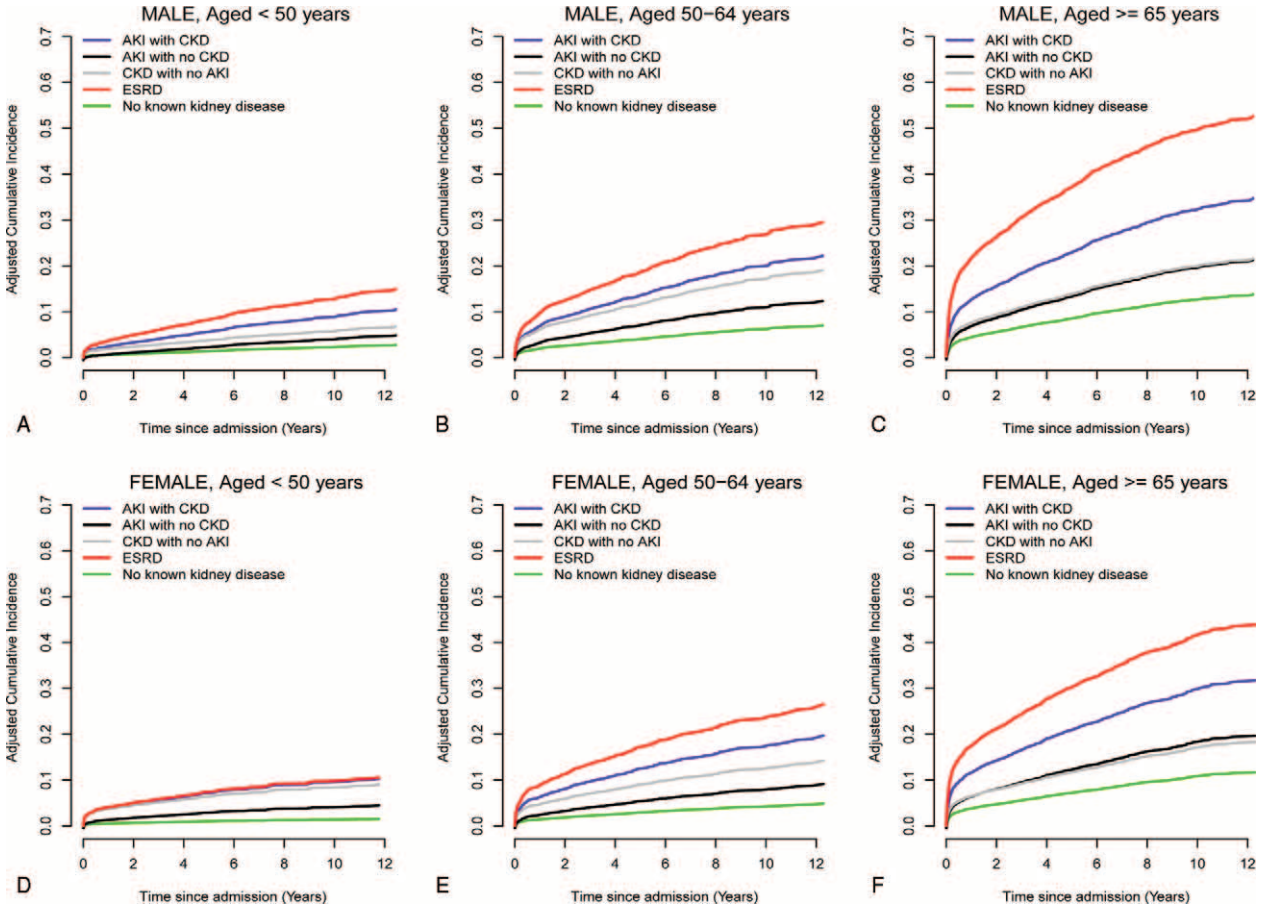

FIGURE 3. Adjusted cumulative incidence curves for cardiovascular mortality by kidney disease status after stratification by age and sex: A, male aged below 50 years; B, female aged below 50 years; C, male aged 50 to 64 years; D, female aged 50 to 64 years; E, male aged at least 65 years; and F, female, aged at least 65 years. All groups with acute or chronic kidney disease have significantly higher hazards ratios compared with no known kidney disease group within each strata, with *P* value less than 0.001, except for CKD with no AKI group for women aged between 50 and 64 years and men aged below 50 years ($P < 0.05$).

Compared with patients with no kidney disease, the adjusted hazard ratios for cardiovascular-specific mortality were significantly higher among patients with kidney disease, ranging from 1.95 (95% CI, 1.80–2.11) for patients with de novo AKI to 5.70 (95% CI, 5.00–6.49) for patients with ESRD before admission. This significant association was preserved in sensitivity analyses with inclusion of individual comorbidities and postoperative complications in the model (Table 3). The adjusted hazards of cardiovascular-specific mortality increased with increasing severity of both AKI and CKD (Table 4). Age, admission comorbidities, and hemoglobin level below 12 g/dL, emergent surgery status, and surgery type were significantly associated with cardiovascular mortality.

For internal validation of the study, we tested the performance of the models in validation cohorts and performed several sensitivity analyses. The multivariable competing risk models performed well with C-index values of 0.84 (95% CI, 0.83–0.85), 0.81 (95% CI, 0.80–0.82), and 0.79 (95% CI, 0.78–0.80) at 1, 5, and 10 years, respectively, in the validation datasets. Similar performance was observed for the competing risk models that included severity of kidney disease stages, with C-index values of 0.85 (95% CI, 0.84–0.86), 0.81 (95% CI, 0.80–0.83), and 0.79 (95% CI, 0.78–0.80) at 1, 5, and 10 years, respectively. No significant difference was found between the C-indices of competing risk models applied to training and validation cohorts ($P > 0.05$). The slight decrease in C-index over time was likely due to the fact that earlier events are easier to predict than later events.[36] Sensitivity analyses demonstrated no significant difference among multivariable models after censoring patients on October 31, 2011, excluding missing causes of death or

TABLE 3. Adjusted Hazard Ratios for Cardiovascular-specific Mortality Using Multivariable Subdistributional Hazards Models

	Model With Charlson Comorbidity Index Score	Model With Individual Comorbidities	Model With Postoperative Complications
	Adjusted Hazard Ratio	Adjusted Hazard Ratio	Adjusted Hazard Ratio
Variables	**(95% Confidence Interval)**	**(95% Confidence Interval)**	**(95% Confidence Interval)**
Kidney disease			
No known kidney disease (reference group)	1	1	1
Acute kidney injury without chronic kidney disease	1.95 (1.80, 2.11)*	1.86 (1.71, 2.01)*	1.58 (1.45, 1.72)*
Acute kidney injury with chronic kidney disease	3.58 (3.22, 3.98)*	3.24 (2.91, 3.61)*	2.86 (2.56, 3.20)*
Chronic kidney disease without acute kidney injury	2.04 (1.68, 2.48)*	1.93 (1.59, 2.34)*	2.02 (1.67, 2.45)*
End- stage renal disease	5.70 (5.00, 6.49)*	6.05 (5.33, 6.87)*	5.11 (4.49, 5.83)*
Age, per 1-year increase	1.04 (1.04, 1.04)*	1.04 (1.03, 1.04)*	1.04 (1.04, 1.04)*
Male (vs female)	1.08 (1.02, 1.15)*	1.09 (1.02, 1.16)*	1.07 (1.003, 1.13)*
African-American ethnicity (vs others)	1.13 (1.03, 1.24)*	1.08 (0.99, 1.19)	1.16 (1.06, 1.27)*
Charlson Comorbidity Index Score			
0 (reference group)	1	NA	1
1	2.05 (1.83, 2.31)*	NA	1.97 (1.75, 2.22)*
2	2.17 (1.94, 2.43)*	NA	2.12 (1.89, 2.38)*
≥3	2.45 (2.19, 2.73)*	NA	2.40 (2.15, 2.68)*
Comorbidities			
Hypertension (yes vs no)	NA	1.10 (1.02, 1.17)*	NA
Diabetes (yes vs no)	NA	1.41 (1.31, 1.52)*	NA
Chronic pulmonary disease (yes vs no)	NA	1.09 (1.01, 1.17)*	NA
Peripheral vascular disease (yes vs no)	NA	1.65 (1.53, 1.78)*	NA
Cerebrovascular disease (yes vs no)	NA	2.07 (1.89, 2.26)*	NA
Congestive heart failure (yes vs no)	NA	2.00 (1.85, 2.17)*	NA
Myocardial infarction (yes vs no)	NA	1.44 (1.32, 1.57)*	NA
Emergent surgery (vs elective)	1.58 (1.48, 1.68)*	1.46 (1.37, 1.56)*	1.50 (1.40, 1.60)*
Surgery type, n (%)			
Specialty surgeries† (reference group)	1	1	1
Cardiothoracic surgery	2.28 (2.08, 2.5)*	1.76 (1.59, 1.94)*	1.86 (1.69, 2.05)*
Neurologic surgery	1.53 (1.38, 1.7)*	1.21 (1.09, 1.36)*	1.28 (1.15, 1.43)*
Noncardiac general surgery	1.46 (1.33, 1.6)*	1.26 (1.15, 1.39)*	1.39 (1.27, 1.53)*
Other surgeries‡	0.59 (0.52, 0.67)*	0.66 (0.58, 0.75)*	0.57 (0.50, 0.65)*
Admission hemoglobin, g/dL			
≥12 (reference group)	1	1	1
<10	1.09 (0.99, 1.19)	1.12 (1.02, 1.23)*	1.03 (0.94, 1.14)
[10,12)	1.13 (1.04, 1.22)*	1.13 (1.04, 1.23)*	1.11 (1.03, 1.21)*
Missing	0.97 (0.89, 1.06)	1.02 (0.93, 1.11)	0.99 (0.92, 1.09)*
Number of postoperative complications§			
0 (reference group)	NA	NA	1
1	NA	NA	1.15 (1.05, 1.25)*
2	NA	NA	1.37 (1.24, 1.51)*
≥3	NA	NA	2.08 (1.91, 2.27)*

*$P < 0.05$.

†Specialty surgeries include orthopedic, gynecological, ear-nose-throat, urology, and plastic surgeries.

‡Other surgeries include trauma, burn, and transplant surgeries.

§Number of postoperative complications sums 6 major complications, including mechanical ventilation for longer than 48 hours, intensive care unit admission, severe sepsis, cardiovascular complications, neurological complications, and wound complications (including mechanical wound complications and surgical infections).

NA indicates not applicable.

TABLE 4. Adjusted Hazard Ratios for Cardiovascular-specific Mortality for Acute and Chronic Kidney Disease Stratified by Severity Stages Using Multivariable Subdistributional Hazards Models

	Model With Charlson Comorbidity Index Score	Model With Individual Comorbidities
	Adjusted Hazard Ratio	Adjusted Hazard Ratio
Variables	**(95% Confidence Interval)**	**(95% Confidence Interval)**
Kidney disease stratified by severity stages		
No known kidney disease	Reference group hazard ratio 1	Reference group hazard ratio 1
Stage 1 acute kidney injury	1.76 (1.62, 1.92)*	1.66 (1.52, 1.82)*
Stage 2 acute kidney injury	2.14 (1.92, 2.39)*	1.97 (1.76, 2.20)*
Stage 3 acute kidney injury	4.01 (3.62, 4.43)*	3.92 (3.53, 4.35)*
Mild chronic kidney disease	1.94 (1.37, 2.75)*	1.78 (1.26, 2.51)*
Moderate chronic kidney disease	1.92 (1.51, 2.44)*	1.79 (1.40, 2.29)*
Severe chronic kidney disease	2.87 (1.66, 4.97)*	3.16 (1.85, 5.39)*
End-stage renal disease	5.73 (5.03, 6.53)*	6.06 (5.34, 6.88)*
Age, per 1-year increase	1.04 (1.04, 1.04)*	1.04 (1.03, 1.04)*
Male (vs female)	1.10 (1.03, 1.17)*	1.11 (1.04, 1.18)*
African-American ethnicity (vs others)	1.15 (1.05, 1.26)*	1.09 (0.997, 1.20)
Charlson comorbidity index score		
0	Reference group hazard ratio 1	NA
1	2.01 (1.79, 2.26)*	NA
2	2.13 (1.90, 2.39)*	NA
≥3	2.52 (2.26, 2.81)*	NA
Comorbidities		
Hypertension (yes vs no)	NA	1.17 (1.09, 1.26)*
Diabetes (yes vs no)	NA	1.46 (1.36, 1.57)*
Chronic pulmonary disease (yes vs no)	NA	1.09 (1.01, 1.17)*
Peripheral vascular disease (yes vs no)	NA	1.70 (1.57, 1.83)*
Cerebrovascular disease (yes vs no)	NA	2.06 (1.89, 2.25)*
Congestive heart failure (yes vs no)	NA	2.00 (1.84, 2.17)*
Myocardial infarction (yes vs no)	NA	1.44 (1.32, 1.57)*
Emergent surgery (vs elective)	1.51 (1.42, 1.62)*	1.4 (1.31, 1.50)*
Surgery type, n (%)		
Specialty surgeries†	Reference group hazard ratio 1	Reference group hazard ratio 1
Cardiothoracic surgery	2.21 (2.02, 2.43)*	1.67 (1.51, 1.84)*
Neurologic surgery	1.52 (1.36, 1.69)*	1.20 (1.07, 1.34)*
Noncardiac general surgery	1.42 (1.29, 1.55)*	1.21 (1.10, 1.33)*
Other surgeries‡	0.57 (0.50, 0.64)*	0.63 (0.56, 0.72)*
Admission hemoglobin, g/dL		
≥12	Reference group hazard ratio 1	Reference group hazard ratio 1
<10	1.10 (1.01, 1.21)	1.13 (1.03, 1.24)*
[10, 12)	1.14 (1.05, 1.23)*	1.14 (1.05, 1.24)*
Missing	0.98 (0.9, 1.07)	1.03 (0.95, 1.13)

*$P < 0.05$.
†Specialty surgeries include orthopedic, gynecological, ear-nose-throat, urology, and plastic surgeries.
‡Other surgeries include trauma, burn, and transplant surgeries.
NA indicates not applicable.

after using different definitions for cardiovascular cause of death and reference creatinine or after imputing missing hemoglobin values ($P > 0.05$ for all comparisons).

DISCUSSION

In a large single-center cohort of surgical patients, both AKI and CKD were associated with up to a 4-fold increase in long-term cardiovascular-specific mortality compared with patients having no kidney disease. This association was independent of the progression to ESRD after discharge, although patients who progressed had larger increase in cardiovascular mortality. The increasing cardiovascular mortality was proportional to the severity of kidney disease, independent of patients' age, sex, comorbidity burden on admission, other postoperative complications, or the type of operation in the cohort that included a wide range of major surgical procedures, including noncardiac and specialty surgeries. The development of postoperative AKI, in either the presence or absence of underlying CKD, was independently associated with long-term cardiovascular-specific mortality. Even patients with mild AKI had a 76% increase in the adjusted hazard for cardiovascular-specific mortality. Whereas de novo AKI was 4 times more common than CKD, occurring in 33% of the cohort, it was associated with a comparable 2-fold increase in cardiovascular-specific mortality compared with patients having no kidney disease. Patients with AKI superimposed on underlying CKD comprised a smaller proportion of AKI patients, but had a markedly increased cumulative cardiovascular-specific mortality rate of 19%, almost as high as patients with ESRD. AKI survivors with no previous CKD had 5-fold increase in the rates of ESRD progression compared with patients having no kidney disease, and this association was strengthened by the presence of pre-existing CKD as previously reported among different patient cohorts.[3,8,11,38] To the best of our knowledge, this is the first study to demonstrate that the cardiovascular-specific mortality even in the absence of the

progression to ESRD is the significant contributor to the excessive long-term mortality after surgery in patients with kidney disease.

Chronic kidney disease, from earlier stages to ESRD, is a well known risk factor for cardiovascular disease. The absolute risk for death increases exponentially with decreasing renal function even among patients without manifest cardiovascular disease.[39,40] After adjusting for traditional cardiovascular risk factors, the risk gradient for cardiovascular mortality increased linearly when eGFR decreased below 75 mL/min/1.73 m^2.[10,41] Men and women with lower levels of kidney function, reflective of CKD, have a substantial and progressive reduction in overall life expectancy, ranging from 1.3 to 21.3 years depending on age and eGFR, specifically due to cardiovascular disease.[9,42,43] Importantly, individuals with earlier stages of CKD are more likely to die of cardiovascular disease than to develop kidney failure and require dialysis.[9,10,41] Once developed, ESRD is associated with an up to 30 times higher cardiovascular mortality compared with the general population.[44] Unfortunately, commonly used guidelines on the management of cardiovascular risk have paid only limited attention to CKD as a notable risk factor rendering cardiovascular disease frequently underdiagnosed and undertreated in these patients.[9]

Our data highlight that patients with postoperative AKI, even in the absence of pre-existing CKD, are susceptible to die from cardiovascular disease at levels comparable to patients with CKD. The relationship between AKI and cardiovascular disease has been recognized in hospitalized, cardiac, and vascular patient populations. Hospitalized patients who recovered from de novo dialysis-requiring AKI are at a high risk of developing nonfatal myocardial infarctions and of needing coronary angiography procedures and coronary artery bypass grafting surgery, independent of their progression to CKD and ESRD.[13] Studies evaluating outcomes after isolated coronary artery bypass grafting surgery accounted for preoperative renal dysfunction in their multivariate survival analyses and have demonstrated that AKI is independently associated with incident congestive heart failure hospitalization and a composite outcome consisting of myocardial infarction, heart failure, stroke, and long-term all-cause mortality.[15,45] Similarly, the occurrence of AKI after coronary angiography is significantly associated with the next hospitalization for congestive heart failure, independent of baseline kidney function and proteinuria, but this association was not significant when myocardial infarctions or cerebrovascular accidents were considered as outcomes.[6] Olsson et al[15] recently demonstrated that AKI without pre-existing CKD was the strongest risk factor for incident hospitalization for congestive heart failure in isolated coronary artery bypass grafting surgical patients. When superimposed on pre-existing CKD, AKI may exacerbate renal dysfunction and expedite the progression to ESRD,[12] rendering these patients more susceptible to cardiovascular death with mortality rates comparable with ESRD patients, as demonstrated in our study. Interestingly, the risk for cardiovascular-specific mortality associated with kidney disease was more pronounced among older individuals, but similar across sexes. Liotta et al demonstrated that the associations between AKI and all-cause long-term mortality were even stronger for women than for men in cardiac surgical patients, who underwent primary, isolated coronary artery bypass grafting surgery.[45]

Because the kidneys act as key regulators of multiple homeostatic mechanisms, kidney-specific risk factors for cardiovascular disease become more relevant with acutely or chronically failing kidneys. Apart from hypertension, renal anemia, and increased vascular stiffness, endothelial dysfunction manifested by reduced cardiac capillary density and impaired coronary dilatory response may be contributory mechanisms for the increased prevalence of left ventricular hypertrophy, myocardial fibrosis, impaired contractility, and the more than 50-fold increase in incidence of sudden cardiac death in CKD patients. Increased activity of the renin-angiotensin system and sympathetic nerve activity further impair endothelial function and worsen systemic inflammation and malnutrition.[46] Unfortunately, standardized follow-up after an episode of AKI is suboptimal in contemporary clinical practice. Less than 50% of patients with the most severe AKI will have a follow-up creatinine measured within the first 3 months of hospitalization, and it is even less likely that follow-up will be obtained after less severe AKI.[47] Among AKI survivors with persistent renal dysfunction at discharge, the referral rates for outpatient nephrology consultation are as low as 11%.[47,48]

We acknowledge the limitation of the retrospective nature of the cohort, but with the use of multivariable adjustments and evaluation of model discrimination on validation datasets, we have attempted to increase the internal validity of the competing risk models. Longitudinal studies involving determination of long-term mortality, and especially cause of death, are not only costly, but increasingly difficult to perform.[23] Although this is a single-center study which may elicit questions of generalizability, the site of the study is a large tertiary care center that receives a large number of referrals from all over the state and hence has a very heterogeneous patient profile over a wide range of procedures. Furthermore, the application of standard survival analysis leads to bias and risk overestimation if competing risks are present and specialized methods as one we used are needed.[35,36] Our multivariable modeling technique is attractive when potentially competing causes of death are present as it allows patient-specific estimates of the absolute risk of the cardiovascular-specific death based on a set of covariates.[34] To our knowledge, no prospective surgical cohort of this size and heterogeneity had concomitant data on both kidney disease and cardiovascular cause of death. We had only limited data on urine output or on patients with AKI and preoperative proteinuria among patients with CKD that could have strengthened our analysis. We used a combination of ICD-9-CM administrative codes and eGFR on admission to define CKD status. A recent systematic review demonstrated that although sensitivity for coded CKD covariates was highly variable, specificity was high, with all studies reporting values above 0.90.[49] We have demonstrated that, although increased, progression to ESRD among AKI patients may not be an only determinant of cardiovascular mortality, just as patients with mild CKD are more likely to die from cardiovascular disease than to progress to ESRD.[9,10,41] Some of the traditional cardiovascular risk factors were not recorded in our database—that is, systolic blood pressure, total cholesterol, high-density lipoprotein, and smoking history—and thus were unable to be included as covariates.[50] Patient cardiovascular comorbidity information, however, was available for previous myocardial infarctions, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes, and hypertension, and each patient's Charlson-Deyo comorbidity index was calculated and included as a model covariate.

CONCLUSIONS

In summary, both AKI and CKD commonly occurred during hospitalization for major surgical procedures and were associated with up to a 4-fold increase in long-term cardiovascular-specific mortality compared with patients having no kidney disease. This association was proportional to the severity of kidney disease, independent of sex, and amplified by age and progression to ESRD. This information speaks of the importance of the preoperative determination of kidney health by applying consensus staging criteria for CKD that uses both eGFR and proteinuria. Similarly, both preoperative and postoperative risk stratification for AKI using clinical scores and urinary biomarkers can allow implementation of

simple and inexpensive preventive strategies in the perioperative period that could prevent or mitigate further decline in kidney function. The appropriate transition of follow-up to the outpatient setting, with emphasis on the prevention of kidney disease progression and mitigation of cardiovascular risk, is almost absent in contemporary practice. Our data present compelling evidence that such an effort is both warranted and justifiable.

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