Acute Kidney Injury and Subsequent Kidney Failure With Replacement Therapy Incidence in Older Adults With Advanced CKD: A Cohort Study of US Veterans

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Rationale & Objective: Advanced age is a major risk factor for chronic kidney disease (CKD) development, which has high heterogeneity in disease progression. Acute kidney injury (AKI) hospitalization rates are increasing, especially among older adults. Previous AKI epidemiologic analyses have focused on hospitalized populations, which may bias results toward sicker populations. This study examined the association between AKI and incident kidney failure with replacement therapy (KFRT) while evaluating age as an effect modifier of this relationship.

Study Design: Retrospective cohort study.

Setting & Participants: 24,133 Veterans at least 65 years old with incident CKD stage 4 from 2011 to 2013.

Exposures: AKI, AKI severity, and age.

Outcomes: KFRT and death.

Analytical Approach: The Fine-Gray competing risk regression was used to model AKI and incident KFRT with death as a competing risk. A Cox regression was used to model AKI severity and death.

Results: Despite a nonsignificant age interaction between AKI and KFRT, a clinically relevant combined effect of AKI and age on incident KFRT was observed. Compared with our oldest age group without AKI, those aged 65-74 years with AKI had the highest risk of KFRT (subdistribution HR [sHR], 14.9; 95% CI, 12.7-17.4), whereas those at least 85 years old with AKI had the lowest (sHR, 1.71; 95% CI, 1.22-2.39). Once Veterans underwent KFRT, their risk of death increased by 44%. A 2-fold increased risk of KFRT was observed across all AKI severity stages. However, the risk of death increased with worsening AKI severity.

Limitations: Our study lacked generalizability, was restricted to ever use of medications, and used inpatient serum creatinine laboratory results to define AKI and AKI severity.

Conclusions: In this national cohort, advanced age was protective against incident KFRT but not death. This is likely explained by the high frequency of deaths observed in this population (51.1%). Nonetheless, AKI and younger age are substantial risk factors for incident KFRT.

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Kidney Med. 6(6):100825. Published online April 16, 2024.

doi: 10.1016/j.xkme.2024.100825

About 15% of the US population has chronic kidney disease (CKD), be it mild, moderate, or severe.[1] Advanced age is a major risk factor for the development of CKD, which has high heterogeneity in disease progression.[2-5] Those aged at least 65 years represent the largest growing age category in the United States and likely experience the greatest CKD burden.[1,6] This is partly attributed to their propensity for having a high prevalence of CKD-associated comorbid conditions such as diabetes mellitus, hypertension, and cardiovascular disease.[3,7] In 2016, nearly a quarter (23.9%) of US Veterans aged at least 65 years had CKD stage 3 or higher.[8] This is likely a reflection of the US Department of Veteran Affairs (VA) older age distribution and increased prevalence of comorbid conditions compared with their civilian counterparts.[9]

Acute kidney injury (AKI), defined as an abrupt period of kidney dysfunction,[10] is a frequent complication of hospitalization, occurring in up to 20% of inpatient stays and in over 40% of patients in intensive care.[11-13] It is associated with mortality, especially in the critically ill patients in whom hospital death rates exceed 50% among those who develop severe forms of AKI.[12,13] According to the US Renal Data System (USRDS), AKI hospitalization rates are increasing,[1] especially among older adults who are at elevated risk given their advanced age, increased use of prescription drugs, large number of comorbid conditions, high exposure to surgical interventions, and a weakening immune system.[14-17] This population is also at risk of subsequent nonrecovery from AKI, resulting in the need for emergent dialysis or worse, long-term dialysis.[15-17] Prior AKI epidemiologic analyses have focused on hospitalized populations, which may bias results toward sicker populations, particularly when results are extrapolated to ambulatory CKD populations. Limitations in data availability are primarily to blame for this because AKI detection requires frequent monitoring of serum creatinine (Scr) levels. Therefore, we propose using a national cohort of older adults in the VA with incident CKD stage 4 to examine the association between AKI and incident kidney failure with replacement therapy (KFRT) while evaluating age as an effect modifier of this relationship.

METHODS

Study Population and Design

Administrative data from the Veterans Health Administration Corporate Data Warehouse were used to assemble a national retrospective cohort of Veterans aged at least 65

PLAIN LANGUAGE SUMMARY

Older adults are at risk of acute kidney injury (AKI) and subsequent nonrecovery from AKI, resulting in long-term dialysis. Hospitalized patients have often been used in the past to study AKI. This could lead to biased conclusions when inferring from sicker populations. That is why we created a national cohort of 24,133 Veterans at least 65 years old with incident chronic kidney disease (CKD) stage 4 to examine the relationship between AKI and age and subsequent kidney failure with replacement therapy (KFRT). The data have showed that AKI and younger age are substantial risk factors for incident KFRT. As for older age, it appears to be protective against KFRT but not death. This is likely explained by the high frequency of deaths observed in our cohort.

years with incident CKD stage 4 from 2011-2013 (Fig 1). Incident CKD stage 4 was defined as having at least 2 consecutive outpatient estimated glomerular filtration rate values between 15-29 mL/min/1.73 m^2 and ≥90 days and ≤1 year apart. The date of the second estimated glomerular filtration rate value was considered the time of cohort entry. The 2009 CKD Epidemiology Collaboration (CKD-EPI) equation was used to estimate kidney function. Veterans were followed until December 31, 2016 or death. The median follow-up time was 3 years. Non-Veterans and those enrolled in the USRDS before cohort entry were excluded. This study was approved by the Institutional Review Board of the Medical University of South Carolina (MUSC) under the protocol number (Pro00035221).

Exposure Definition

AKI after incident CKD stage 4 diagnosis was defined according to the modified KDIGO AKIN (Kidney Disease: Improving Global Outcomes Acute Kidney Injury Network) definition and staging system and coded as a binary variable. The use of these criteria also determined the severity of the first AKI experienced after cohort entry. There are 3 stages of AKI severity, with the third being the most severe and least likely to show recovery. AKI severity was categorized into 4 groups: no AKI and AKI stages 1, 2, and 3. Because of the time constraint in defining AKI (≤7 days), we were limited to inpatient Scr laboratory results. Baseline Scr was defined as the median outpatient Scr 7-365 days before hospitalization.

Outcome Definition

KFRT was defined as the initiation of dialysis and/or receipt of kidney transplant as determined by entry into the USRDS registry. Patients who recovered from an AKI that required dialysis for days or weeks during an inpatient stay were not included in the KFRT definition. All-cause death was considered a competing risk. The date of death during follow-up was obtained from the Master Veterans Health Administration Vital Status file, which contains mortality data from both VA and non-VA sources. Both KFRT and death were coded as binary variables. Time to death was defined as the difference in days between the date of death and the date of cohort entry, whereas time to KFRT was defined as the difference in days between the date of first dialysis or transplant and the date of cohort entry. For Veterans who remained alive without KFRT, the difference between the study end date and the date of cohort entry was used to define the censoring times for death and KFRT. Veterans who died before developing KFRT were censored for KFRT at the time of their death.

Covariate Definitions

AKI history, sex assigned at birth, service-connected disability of at least 50% (SCD ≥ 50%), rural residence, and medication use were coded as binary variables. AKI history was defined as having at least 1 inpatient International Classification of Diseases, Ninth Revision diagnosis for AKI (584.x) in the 2 years before cohort entry. Age was considered both a continuous and categorical variable. Race-ethnicity was categorized into 4 groups: non-Hispanic White (NHW), non-Hispanic Black (NHB), Hispanic, and other (ie, Asian, American Indian or Alaska Native, or Native Hawaiian or other Pacific Islander). Health care use and access metrics were obtained from the Planning Systems Support Group Geocoded Enrollee files. Veterans living in rural or highly rural areas were designated a rural residence. Drive distance and time to the nearest primary care were categorized into quartiles. Inpatient and outpatient International Classification of Diseases, Ninth Revision codes 2 years before cohort entry were used to identify and calculate a weighted sum of all 30 Elixhauser comorbid conditions resulting in a continuous score measure for comorbid condition burden. A 10-point change in the Elixhauser comorbidity burden score was used to detect a clinically meaningful change in the models.

Information on medication use was obtained from the Pharmacy Managerial Cost Accounting National Data Extract. Select medications had to have been prescribed at least once in the 2 years before cohort entry to be considered in the study. Nonsteroidal anti-inflammatory drugs (NSAIDs) were defined according to the VA drug class *MS102*. VA drug classes *CV701*-*CV704* and *CV709* were used to determine diuretic intake. Angiotensin II receptor blockers (ARBs) and or angiotensin-converting enzyme (ACE) inhibitors were identified using the following VA drug classes: *CV800*, *CV805*, *CV400*, and *A1530*.

Statistical Analysis

Appropriate summary descriptive statistics were computed based on data type and distribution. Categorical variables are expressed as percentages and were compared using the χ^2 test. Normally distributed continuous variables are presented as mean ± standard deviation (SD) and compared

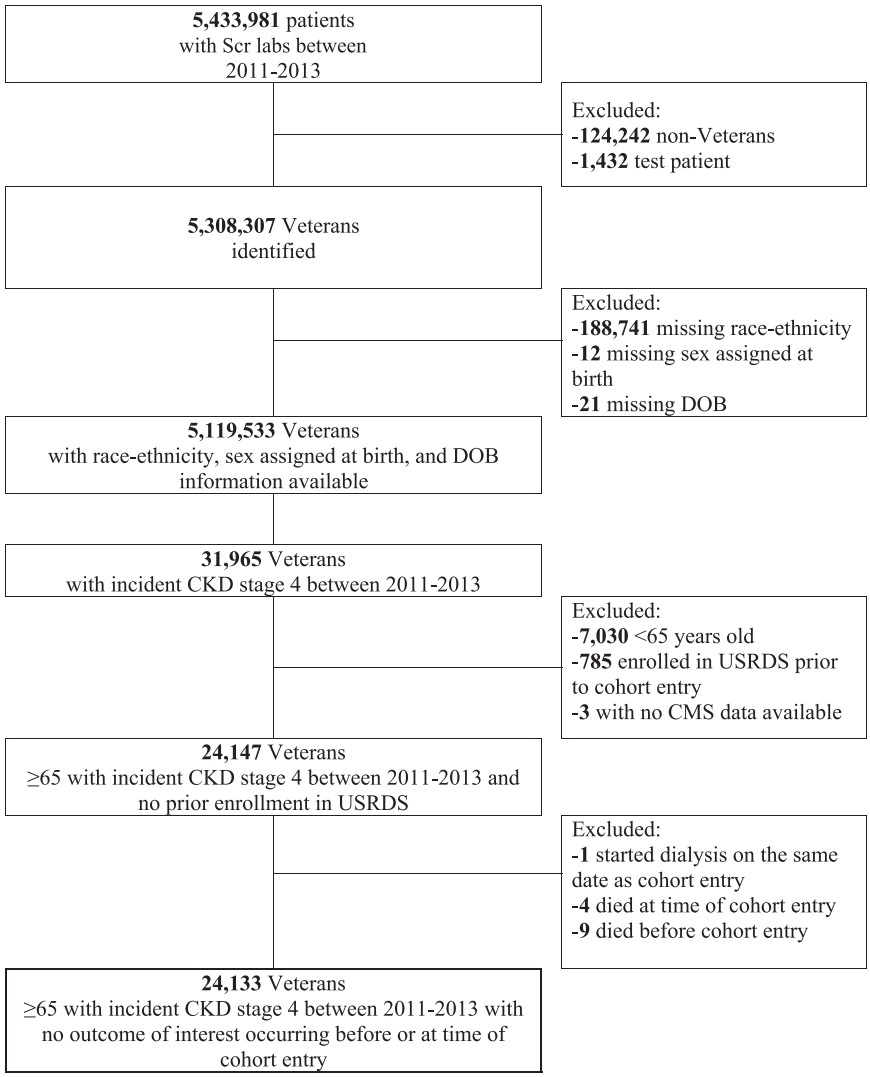

Figure 1. Flowchart of study population and sample size. CKD, chronic kidney disease; CMS, Centers for Medicare and Medicaid Services; DOB, date of birth; Scr, serum creatinine; USRDS, United States Renal Data System.

using the *t* test, whereas nonnormally distributed continuous variables are expressed as medians with interquartile ranges and were compared using the Mann-Whitney U test. The Fine-Gray competing risk regression model was used to determine the association between AKI and incident KFRT while evaluating age as an effect modifier by including an interaction term in the model.[18] AKI severity (model 1) and the combined effect of AKI and age on KFRT (model 2) are reported. The following covariates selected a priori were adjusted for in the model: AKI history, age, sex assigned at birth, race-ethnicity, SCD ≥ 50%, rural residence, drive distance and time to the nearest primary care, the Elixhauser comorbidity burden score, and medication use. Veterans who reached the end of the study without having either the event of interest (KFRT) or the competing event (death) were censored. A Cox proportional hazards model was performed with death as the primary outcome and AKI severity as the main exposure while including KFRT as a time-varying variable. The same covariates as in the competing risk regression (model 1) were adjusted for. SAS Enterprise Guide 8.2 (SAS Institute, Inc) was used to assemble the national retrospective cohort in the VA Informatics and Computing Infrastructure, VINCI. All analyses were performed using RStudio version 4.0.5 (2021-03-31) and the R packages, *KMsurv*, *survival*, and *cmprsk*. A 95% confidence interval (95% CI) that did not cross 1 or a $P < 0.05$ was considered statistically significant.

RESULTS

We identified a total of 24,133 older Veterans with incident CKD stage 4 between 2011-2013, of whom 17.5% experienced at least one AKI after cohort entry (Table 1). The median time to AKI from cohort entry was 1.1 years. The median time was 0.4 years from AKI to KFRT and 0.9 years from AKI to death. The median age of our Veteran cohort was 80 years. Those who had an AKI after cohort entry tended to be younger, with a median age of 75 years.

Table 1. Baseline Descriptive Characteristics of National Retrospective Cohort of Older Veterans Aged at Least 65 Years With Incident CKD Stage 4 From 2011-2013 Stratified by AKI Status

	Total	AKI	No AKI	
	N = 24,133	n = 4,221 (17.5%)	n = 19,912 (82.5%)	*P*
Demographics				
Age, median (IQR)	80 (71-86)	75 (68-83)	80 (73-86)	<0.001[a]
Age (y), n (%)				<0.001[b]
65-74	7,883 (32.7%)	2,016 (47.8%)	5,867 (29.5%)	
75-84	9,145 (37.9%)	1,416 (33.5%)	7,729 (38.8%)	
≥85	7,105 (29.4%)	789 (18.7%)	6,316 (31.7%)	
Male, n (%)	23,697 (98.2%)	4,151 (98.3%)	19,546 (98.2%)	0.4[b]
Race-ethnicity, n (%)				<0.001[b]
NHW	19,569 (81.1%)	2,969 (70.3%)	16,600 (83.4%)	
NHB	3,216 (13.3%)	948 (22.5%)	2,268 (11.4%)	
Hispanic	806 (3.3%)	191 (4.5%)	615 (3.1%)	
Other	542 (2.3%)	113 (2.7%)	429 (2.1%)	
SCD ≥ 50%, n (%)	6,146 (25.5%)	1,376 (32.6%)	4,770 (24.0%)	<0.001[b]
Comorbid condition burden				
Baseline eGFR, median (IQR)	26.2 (23-28.3)	26.2 (23.1-28.3)	26.0 (22.5-28.2)	<0.001[a]
AKI severity, n (%)				<0.001[b]
No AKI	19,912 (82.5%)	0 (0.0%)	19,912 (100.0%)	
AKI stage 1	2,905 (12.1%)	2,905 (68.8%)	(0.0%)	
AKI stage 2	1,044 (4.3%)	1,044 (24.7%)	(0.0%)	
AKI stage 3	272 (1.1%)	272 (6.5%)	(0.0%)	
AKI history, n (%)	3,760 (15.6%)	1,542 (36.5%)	2,218 (11.1%)	<0.001[b]
Elixhauser comorbidity burden score, mean (SD)	**4.8 (7.7)**	**6.7 (9.2)**	**4.4 (7.2)**	**<0.001**[c]
Use and access metrics				
Rural residence, n (%)	9,994 (41.4%)	1,488 (35.3%)	8,506 (42.7%)	<0.001[b]
Missing	58 (0.2%)	9 (0.2%)	49 (0.3%)	
Drive distance to nearest primary care, n (%)				<0.001[b]
0-5 miles	6,328 (26.2%)	1,278 (30.3%)	5,050 (25.4%)	
6-11 miles	6,163 (25.5%)	1,109 (26.3%)	5,054 (25.4%)	
12-22 miles	5,650 (23.4%)	898 (21.3%)	4,752 (23.9%)	
≥23 miles	5,737 (23.8%)	890 (21.0%)	4,847 (24.3%)	
Missing	255 (1.1%)	46 (1.1%)	209 (1.0%)	
Drive time to nearest primary care, n (%)				<0.001[b]
0-10 miles	6,968 (28.9%)	1,406 (33.3%)	5,562 (27.9%)	
11-16 miles	5,100 (21.1%)	920 (21.8%)	4,180 (21.0%)	
17-28 miles	5,961 (24.7%)	963 (22.8%)	4,998 (25.1%)	
≥29 miles	5,849 (24.2%)	886 (21.0%)	4,963 (24.9%)	
Missing	255 (1.1%)	46 (1.1%)	209 (1.1%)	
Miles to nearest primary care, median (IQR)	11 (5-22)	9 (4-19)	11 (5-22)	<0.001[a]
Minutes to nearest primary care, median (IQR)	16 (10-28)	15 (9-25)	17 (10-29)	<0.001[a]
Medication use				
NSAIDs, n (%)	3,268 (13.5%)	817 (19.4%)	2,451 (12.3%)	<0.001[b]
Diuretics, n (%)	15,820 (65.6%)	3,399 (80.5%)	12,421 (62.4%)	<0.001[b]
ARBs and/or ACEis, n (%)	**16,784 (69.6%)**	**3,442 (81.5%)**	**13,342 (67.0%)**	**<0.001**[b]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KFRT, kidney failure with replacement therapy; NHW, non-Hispanic White; NHB, non-Hispanic Black; NSAID, nonsteroidal anti-inflammatory drug; SCD ≥ 50%, service-connected disability of at least 50%; SD, standard deviation.
[a]Mann-Whitney *U* test.
[b]χ^2 test.
[c]*t* test.

Table 2. Reporting of Outcomes

Outcomes	Total n (%)	AKI n (%)	No AKI n (%)	*P*
KFRT	3,506 (14.5%)	1,100 (26.1%)	2,406 (12.1%)	<0.001[a]
Died before KFRT	12,334 (51.1%)	2,303 (54.6%)	10,031 (50.4%)	<0.001[a]
Alive without KFRT	8,293 (34.4%)	818 (19.4%)	7,475 (37.5%)	<0.001[a]

Abbreviations: AKI, acute kidney injury; KFRT, kidney failure with replacement therapy.
[a]χ^2 test.

Nearly half (47.8%) of the AKI group were aged 65-74 years, whereas in the non-AKI group, only 29.5% were 65-74. Most Veterans were male (98.2%) and NHW (81.1%). However, a higher proportion of NHBs comprised the AKI group than the non-AKI group (22.5% vs 11.4%). A quarter (25.5%) of Veterans and nearly a third (32.6%) of those with an AKI had a SCD of ≥50%. Among the AKI group, 68.8% of the AKIs were stage 1, 24.7% were stage 2, and 6.5% were stage 3 in severity. More Veterans in the AKI group than in the non-AKI group (36.5% vs 11.1%) had a history of AKI in the 2 years precursing cohort entry. Similarly, the average comorbid condition burden was greater in the AKI than non-AKI group (6.7 vs 4.4). The Elixhauser comorbidity burden score ranged from −14 to 62 in the total population and the non-AKI group, whereas in the AKI group it ranged from −9 to 51. About 41.4% of Veterans lived in a rural or highly rural area. Fewer Veterans in the AKI group had a rural residence than those in the non-AKI group (35.3% vs 42.7%). The median number of miles driven to the nearest primary care was 9 miles in the AKI group and 11 miles in the non-AKI group. The median drive time to the nearest primary care was 15 minutes in the AKI group and 17 minutes in the non-AKI group. A higher proportion of Veterans in the AKI group used NSAIDs (19.4% vs 12.3%), diuretics (80.5% vs 62.4%), and ARBs and/or ACE inhibitors (81.5% vs 67%) relative to their non-AKI counterparts.

About a quarter (26%) of Veterans in the AKI group and 12.1% in the non-AKI group progressed to KFRT (Table 2). Over half (51.1%) of our cohort died before developing KFRT during the study period, 14.5% progressed to KFRT, and a third (34.4%) were alive without KFRT. Less than 1% (n = 15) of those who progressed to KFRT received a kidney transplant. The remaining 99% (n = 3,491) received dialysis. The AKI group had the highest proportion of deaths (54.6% vs 50.4%) and lowest proportion of living participants without KFRT (19.4% vs 37.5%) compared with the non-AKI group. Irrespective of AKI status, more Veterans died than progressed to KFRT according to the data as shown in the unadjusted cumulative incidence plot (Fig 2). However, those who experienced an AKI after cohort entry had a greater incidence of KFRT than their non-AKI counterparts.

AKI severity was associated with an increased risk of KFRT (Table 3, model 1). Roughly all 3 AKI severity stages had a similar 2-fold increased risk of KFRT when compared with no AKI. Increasing age was inversely associated with the risk of KFRT. The youngest age group had the highest risk of KFRT (subdistribution hazard ratio [sHR], 7.43; 95% CI, 6.51-8.49) relative to the oldest age group. A 10-point change in comorbid condition burden was associated with a 15% decreased risk of KFRT. Veterans with a history of AKI had a 34% lower risk of KFRT than those without a history of AKI. Conversely, the risk of KFRT was 2 times higher in males than in females. The risk

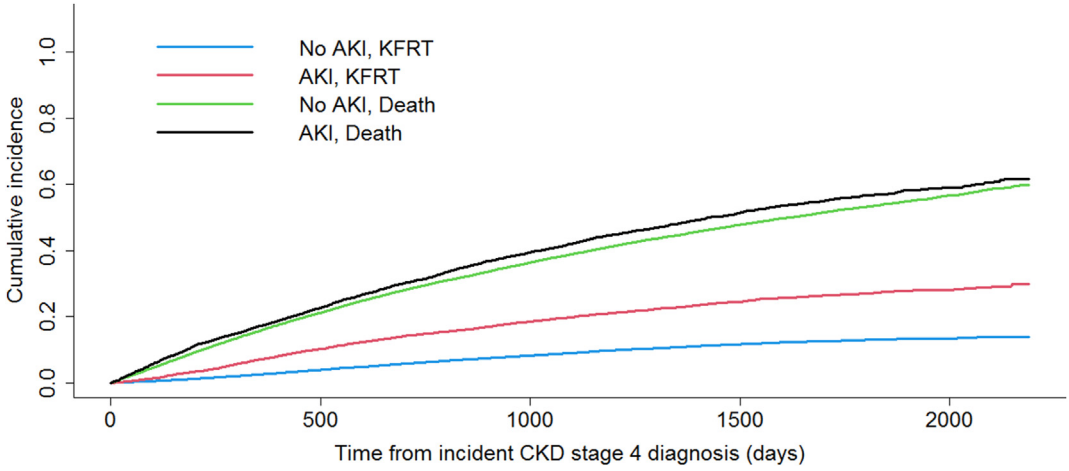

Figure 2. Unadjusted cumulative incidence plot of KFRT and death among a retrospective cohort of older Veterans aged at least 65 years by AKI status from time of incident CKD stage 4 diagnosis. AKI, acute kidney injury; CKD, chronic kidney disease; KFRT, kidney failure with replacement therapy.

Table 3. Adjusted sHRs and 95% CIs for KFRT With Death as a Competing Risk

	Model 1		Model 2	
	sHR	95% CI	sHR	95% CI
Main exposure				
AKI severity				
No AKI (Referent)	1.00	—	—	—
AKI stage 1	1.95	(1.79-2.12)	—	—
AKI stage 2	2.14	(1.89-2.43)	—	—
AKI stage 3	1.91	(1.47-2.48)	—	—
AKI and age categories				
≥85 y – No AKI (Referent)	—	—	1.00	—
≥85 y – AKI	—	—	1.71	(1.22-2.39)
75-84 y – No AKI	—	—	3.38	(2.90-3.93)
75-84 y – AKI	—	—	6.14	(5.10-7.38)
65-74 y – No AKI	—	—	7.10	(6.12-8.23)
65-74 y – AKI	—	—	14.9	(12.7-17.4)
Demographics				
Age (y)				
≥85 (Referent)	1.00	—	—	—
75-84	3.40	(2.96-3.90)	—	—
65-74	7.43	(6.51-8.49)	—	—
Male	2.02	(1.40-2.91)	—	—
Race-ethnicity				
NHW (Referent)	1.00	—	1.00	—
NHB	1.86	(1.71-2.02)	1.86	(1.71-2.03)
Hispanic	1.85	(1.60-2.15)	1.86	(1.60-2.16)
Other	1.57	(1.30-1.90)	1.57	(1.29-1.90)
SCD ≥ 50%	1.13	(1.05-1.21)	1.13	(1.05-1.21)
Comorbid condition burden				
Elixhauser comorbidity burden score[a]	0.85	(0.81-0.90)	0.85	(0.81-0.90)
AKI history	0.66	(0.60-0.73)	0.66	(0.60-0.72)
Use and access metrics				
Rural residence	1.02	(0.93-1.12)	1.02	(0.93-1.12)
Drive distance to nearest primary care				
0-5 miles (Referent)	1.00	—	1.00	—
6-11 miles	1.32	(1.15-1.51)	1.32	(1.15-1.51)
12-22 miles	1.25	(1.04-1.51)	1.26	(1.04-1.52)
≥23 miles	1.30	(1.03-1.65)	1.31	(1.03-1.66)
Drive time to nearest primary care				
0-10 min (Referent)	1.00	—	1.00	—
11-16 min	0.87	(0.76-1.00)	0.87	(0.76-1.00)
17-28 min	0.92	(0.77-1.10)	0.92	(0.77-1.09)
≥29 min	0.83	(0.66-1.04)	0.82	(0.65-1.04)
Medication use				
NSAIDs	0.82	(0.74-0.90)	0.82	(0.74-0.90)
Diuretics	1.02	(0.94-1.11)	1.02	(0.95-1.11)
ARBs and/or ACEis	0.93	(0.86-1.01)	0.93	(0.86-1.01)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; CI, confidence interval; KFRT, kidney failure with replacement therapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; NSAID, nonsteroidal anti-inflammatory drug; SCD ≥ 50%, service-connected disability of at least 50%; sHR, subdistribution hazard ratio.
[a]The change in HR for the Elixhauser comorbidity burden score reflected a 10-point change.

of KFRT among NHBs and Hispanics was 86% and 85% higher than among their NHW counterparts, respectively. Other racial–ethnic groups had a 57% increased risk of KFRT compared with NHWs. A SCD of ≥50% was associated with an elevated risk of KFRT (sHR, 1.13; 95% CI, 1.05-1.21). Neither a rural residence nor drive time to the nearest primary care was associated with KFRT but drive distance to nearest primary care was. Among medications used, only NSAIDs were significantly associated with a reduced risk of KFRT (sHR, 0.82; 95% CI, 0.74-0.90).

Because risk of KFRT did not appear to vary based on AKI severity, we modeled AKI as a binary variable and examined whether age modified the effect of AKI on incident KFRT. Although we did not observe a statistically

significant interaction ($P = 0.08$) between AKI and age, we remained interested in the combined effect of AKI and age on KFRT incidence (Table 3, model 2). Veterans aged 65-74 years with AKI had a nearly 15-fold increased risk of KFRT, whereas those aged 65-74 years without AKI had a 7.1-fold increased risk of KFRT compared to Veterans at least 85 years old with no AKI. Veterans aged 75-84 years with AKI and those without AKI had a 6.1-fold and nearly 3.4-fold increased risk of KFRT compared to those aged at least 85 years without AKI, respectively. Veterans aged at least 85 years with AKI had a 1.7-fold increased risk of KFRT than their same-aged counterparts with no AKI. Estimates for the remaining covariates were similar between models 1 and 2 as evidenced by the 95% CIs.

The risk of death increased significantly with increasing AKI severity (AKI stage 1 HR, 1.25; 95% CI, 1.19-1.31; AKI stage 2 HR, 1.48; 95% CI, 1.38-1.59; AKI stage 3 HR, 1.79; 95% CI, 1.57-2.04) when compared with no AKI (Table 4). We also observed a 44% increase in the risk of the death among those who progressed to KFRT at any given time during our study period than those who did not progress to KFRT. Those aged 65-74 years had a lower risk of death than those aged at least 85 years (HR, 0.44; 95% CI, 0.42-0.46). A 10-point increase in comorbid condition burden was associated with a 16% increased risk of death. Veterans with a history of AKI had a 39% higher risk of death than those who did not. Similarly, the risk of death relative to females was 1.5 times higher in males. The risk of death among NHBs and Hispanics was 24% and 25% lower than among NHWs, respectively. Other racial–ethnic groups had a 13% reduced risk of death compared with NHWs. A SCD of ≥50% was associated with a decreased risk of death (HR, 0.85; 95% CI, 0.82-0.89). Among medications used, NSAIDs (HR, 0.87; 95% CI, 0.83-0.92) as well as ARBs and or ACE inhibitors (HR, 0.88; 95% CI, 0.85-0.91) were associated with a reduction in death risk. Conversely, Veterans using diuretics had a 30% increased risk of death than nonusers.

Table 4. Adjusted HRs and 95% CIs for Death

	HR	95% CI
KFRT	1.44	(1.38-1.50)
Main exposure		
AKI severity		
No AKI (Referent)	1.00	—
AKI stage 1	1.25	(1.19-1.31)
AKI stage 2	1.48	(1.38-1.59)
AKI stage 3	1.79	(1.57-2.04)
Demographics		
Age (y)	1.00	—
≥85 (Referent)	0.63	(0.60-0.65)
75-84	0.44	(0.42-0.46)
65-74		
Male	1.51	(1.32-1.72)
Race-ethnicity		
NHW (Referent)	1.00	—
NHB	0.76	(0.72-0.80)
Hispanic	0.75	(0.68-0.83)
Other	0.87	(0.78-0.98)
SCD ≥ 50%	0.85	(0.82-0.89)
Comorbid condition burden		
Elixhauser comorbidity burden score[a]	1.16	(1.13-1.18)
AKI history	1.39	(1.33-1.45)
Use and access metrics		
Rural residence	0.97	(0.93-1.01)
Drive distance to nearest primary care		
0-5 miles (Referent)	1.00	—
6-11 miles	0.98	(0.92-1.05)
12-22 miles	1.00	(0.92-1.10)
≥23 miles	1.02	(0.91-1.14)
Drive time to nearest primary care		
0-10 min (Referent)	1.00	—
11-16 min	1.00	(0.94-1.07)
17-28 min	0.96	(0.88-1.04)
≥29 min	0.91	(0.82-1.02)
Medication use		
NSAIDs	0.87	(0.83-0.92)
Diuretics	1.30	(1.25-1.35)
ARBs and/or ACEis	0.88	(0.85-0.91)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AKI, acute kidney injury; CI, confidence interval; HR, hazard ratio; KFRT, kidney failure with replacement therapy; NHB, non-Hispanic Black; NHW, non-Hispanic White; NSAID, nonsteroidal anti-inflammatory drug; SCD ≥ 50%, service-connected disability of at least 50%.
[a]The change in HR for the Elixhauser comorbidity burden score reflected a 10-point change.

DISCUSSION

Though we did not find a significant interaction between AKI and age ($P = 0.08$) with risk of KFRT, our adjusted model that included death as a competing risk demonstrated a clinically relevant combined effect of AKI and age on KFRT incidence in older US Veterans with incident CKD stage 4. We noted a decreasing trend in the risk of KFRT with increasing age strata. When compared with our oldest age group without AKI, those aged 65-74 years with AKI had the highest risk of KFRT, whereas those aged at least 85 years with AKI had the lowest. This is likely a consequence of age attenuating the risk of KFRT in older patients with advanced CKD who are more likely to die from other competing causes. Therefore, age may act as a semicompeting risk as evidenced by the Kidney Failure Risk Equation.[19] Nonetheless, AKI remains a significant and independent contributor to disease progression. Based on a large, representative sample of Medicare beneficiaries, Ishani et al[20] observed a multiplicative effect of AKI and CKD on KFRT in which those who had both conditions had a 41.2-fold higher risk of KFRT than those who had neither. AKI alone was associated with a 13-fold increased risk of KFRT, whereas CKD alone had an 8.4-fold increased risk of KFRT when compared with no AKI and no CKD.[20]

The unadjusted cumulative incidence for death was higher among the AKI than non-AKI group. Similar results were observed for the outcome KFRT, but overall, the

unadjusted cumulative incidence for KFRT was lower than for death irrespective of AKI status. Several studies have observed slower losses of kidney function in older patient populations.[21,22] This may be explained by their increased likeliness of dying than progressing to KFRT.

We observed an upward trend in the risk of death with increasing AKI severity. This link between AKI severity and death was consistent with a cohort of Veterans with diabetes who underwent noncardiac surgery.[23] However, even the mildest form of AKI, which made up most of the AKI severity cases in our cohort, was associated with an increased risk of death. For those who developed KFRT at any given time during the study period, their risk of death doubled compared with those who did not. Although dialysis prolongs the lives of many, it has been associated with high mortality rates, especially during the first several months of initiation.[24] In the United States, nearly a quarter of patients, at least 80 years old and 10% of patients 65-79 years old die within the first 3 months of starting dialysis.[25]

Our study found AKI history to be strongly associated with an increased risk of death but not KFRT. Despite a history of AKI being a well-known characteristic of KFRT incidence,[24,26,27] the protective effect of AKI history in our analysis is likely explained by more Veterans dying before developing KFRT.

NSAID use significantly reduced the risk of KFRT as well as death when compared with no use. Similar findings were noted in Medicare part D beneficiaries with or without CKD.[28] Ever users of NSAIDs versus nonusers had a significantly lower risk of death but not KFRT.[28] However, a protective effect against incident KFRT was observed in long-term users of NSAIDs (91-180 days) when compared with nonusers.[28] Chronic pain is prevalent in both older adults and in patients with CKD.[28-31] Perhaps our findings demonstrate the potential benefit of pain relief with NSAIDs despite their well-described nephrotoxic effects.[28]

Given their cardio- and renoprotective properties,[32] users of ARBs and or ACE inhibitors had a significantly lower risk of death than nonusers. Though nonsignificant, the risk of KFRT was lower in Veterans who used ARBs and or ACE inhibitors than those who did not. In contrast, diuretics were associated with an increased risk of death. Diuretics are commonly used to treat volume overload in CKD patients, which is associated with anemia, hypertension, proteinuria, arterial stiffness, and inflammation.[33,34] It is possible that diuretic use is an indicator of increased morbidity and hence the observed higher risk of death among those who use them than those who do not.

There were several limitations in our study. First, our findings lacked generalizability. Second, observational studies such as ours are vulnerable to confounding and thus cannot be used to demonstrate causality. Though we used entry into the USRDS registry to define incident KFRT, we were unable to identify patients who were eligible for KFRT but had not started or refused to undergo treatment or were transitioned to palliative care. This lack of information could have influenced our results. Third, our analysis was restricted to ever use of medications. NSAID use often occurs over-the-counter and thus is unlikely to be tracked. This could have led to misclassification bias in our analysis of NSAID use, which may explain the protective effect we observed despite their nephrotoxic history. Fourth, our study was subject to immortal time bias, meaning patients were considered immortal or unable to experience the outcome of interest between the time from cohort entry to AKI. Finally, we were limited to inpatient Scr laboratory results to define our exposure of interest: first AKI after cohort entry. Despite this, we were able to obtain information on AKI severity and detect mild forms of AKI severity. Previous studies of administrative data have historically relied on diagnostic codes to identify AKI cases, which often represent severe forms of AKI and cannot objectively quantify severity. Most studies of hospitalized patients with AKI assign a baseline Scr at the time of admission, which may not reflect stable levels of kidney function. Because the VA is the largest integrated health care system, it provides ample data on patients long before their AKI event thus enabling us to access outpatient Scr levels before hospital admission to determine an appropriate baseline kidney function.

Management of AKI is limited and often begins after an AKI has occurred. Most of it is supportive, and the proper course of action often relies on the elimination of the suspected agitator, if possible, as in the case of removing prescription drugs with nephrotoxic properties to stop any further declines in kidney function.[35] The only treatment intervention is dialysis if AKI progresses to a more severe form.[36] This puts patients at risk of long-term dialysis if they fail to recover.[37] Our findings helped identify CKD patients at risk of incident KFRT. Though death was far more frequent than KFRT in this population, our national cohort study showed that the combined effect of AKI and age is a substantial risk factor for incident KFRT in older US Veterans with advanced CKD. Preventative measures such as more frequent visits to nephrology care to mitigate the observed poor prognoses associated with AKI in older adults with pre-existing CKD should be considered.

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Support: This research was supported, in part, by the National Center for Advancing Translational Sciences, National Institutes of Health, under Grant Numbers TL1 TR001451 & UL1 TR001450 and by VA Health Services Research and Development (HSR&D) HX001229 & HX003577-01A2/SDR 21-226-3 and the Charleston Health Equity and Rural Outreach Innovation Center (HEROIC).

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgments: Support for VA/CMS Data provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development Service, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004).

Patient Protections: This research was approved by the Institutional Review Board for Human Research at the Medical University of South Carolina (MUSC) under the protocol number (Pro00035221).

Peer Review: Received September 8, 2023, as a submission to the expedited consideration track. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form January 15, 2024.

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