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Acute Kidney Injury Recovery Pattern and Subsequent Risk of Chronic Kidney Disease: An Analysis of Veterans Administration Data

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Abstract

Background: Studies suggest an association between acute kidney injury (AKI) and long-term risk of chronic kidney disease (CKD), even following apparent renal recovery. Whether pattern of renal recovery predicts kidney risk following AKI is unknown.

Study Design: Retrospective cohort.

Setting and Participants: Patients in the Veterans Health Administration in 2011 hospitalized (> 24 hours) with at least two inpatient serum creatinine measurements, baseline eGFR > 60 ml/min/1.73m² and no diagnosis of CKD or ESRD: 17,049 with AKI (16.3%) and 87,715 without.

Predictor: Pattern of recovery to creatinine within 0.3 mg/dl of baseline after AKI: within 2 days (fast), between 3 and 10 days (intermediate), and no recovery by 10 days (slow or unknown).

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Contributions: research idea and study design: MH, DES, VS, KZ, BG, RS, TB, CH, NP, MEP, DW; data acquisition: KZ; data analysis and interpretation: MH, DES, VS, KZ, BG, RS, TB, CH, NP, MEP, DW; statistical analysis: DES, BG; supervision and mentorship: VS, RS, CH, NP, MEP, DW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DES takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Outcome: Stage 3 or higher CKD, defined as 2 outpatient eGFRs <60 ml/min/1.73m² at least 90 days apart or a CKD diagnosis, dialysis, or transplant.

Measurements: Risk of CKD was modeled using modified Poisson regression and time to death-censored CKD modeled using Cox proportional hazards regression, both stratified by stage of AKI.

Results: Most patients' AKI episodes were Stage 1 (91%) and 71% recovered within two days. At one year, 18.2% had developed CKD (AKI: 31.8%, non-AKI: 15.5%, $p<.001$). In stage 1, the adjusted relative risk ratios (RR) for Stage 3 or higher CKD were 1.43 (95% CI 1.39–1.48), 2.00 (95% CI 1.88–2.12), and 2.65 (2.51–2.80) for fast, intermediate, and slow/unknown recovery. A similar pattern was observed in subgroup analyses incorporating albuminuria and sensitivity analysis of death-censored time to CKD.

Limitations: Variable timing of follow-up and mostly male veteran cohort may limit generalizability.

Conclusions: Patients who develop AKI during a hospitalization are at substantial risk for development of CKD by one year following hospitalization and timing of AKI recovery is a strong predictor, even for the mildest forms of AKI.

Keywords

Renal recovery; acute kidney injury outcomes

Introduction

Acute kidney injury (AKI) is a common and frequently devastating clinical syndrome associated with hospital mortality rates approaching 25% overall and exceeding 50% in severe cases.^{1–3} Among survivors, severe AKI requiring dialysis can result in non-recovery or incomplete recovery of renal function; in other words, end-stage renal disease (ESRD) or chronic kidney disease (CKD) respectively.⁴ Recently, there has been increasing recognition that even AKI patients with apparent complete recovery remain at risk for long-term renal complications.^{5–7}

While studies have demonstrated an association between moderate-to-severe forms of AKI and subsequent renal complications, less is known about the prognostic implications of milder forms of AKI, including those with relatively rapid recovery of renal function.⁸ Yet mild AKI makes up the majority of AKI cases and is often unrecognized or dismissed as a benign event.⁹ Follow-up renal evaluation of these patients is likely quite infrequent, considering the low rates of follow-up even among patients with more severe forms of AKI.¹⁰ Identifying patients at risk for long-term complications is therefore an important public health goal; indeed, one of the objectives of Healthy People 2020 is to increase the proportion of AKI patients receiving follow-up renal evaluation.¹¹

Until recent development of consensus definitions for AKI,¹² a particular hindrance to examining AKI outcomes has been the lack of uniformly applied AKI definitions.¹³ The majority of early studies relied on diagnoses in administrative claims data, which are known to be variably applied and inherently biased towards more severe cases of AKI.¹⁴

Conversely, most studies with available clinical data have had limitations including being relatively small and regional, unable to account for key confounding factors such as proteinuria, and/or lack of a non-AKI comparison group.^{5, 6, 15–17} Such studies also do not permit detailed characterization of renal recovery patterns. Using data from the U.S. Veterans Health Administration (VHA or VA) provides a unique opportunity to examine AKI on a national level using both administrative and clinical data, allowing the application of consensus AKI definitions.

The goal of this study was to characterize the risk of adverse renal outcomes following hospitalization for AKI in patients without pre-existing CKD (*de novo* AKI). In particular, we focused on patterns of AKI recovery, which typically cannot be captured in studies using administrative data. We hypothesized that longer AKI recovery times would be associated with significant increased risk for renal complications.

Methods

Study Population

A 100% national data sample from the VHA system for fiscal years (FY; October through September) 2010 to 2012 was used for the study. The VHA is the largest integrated health care system in the US.¹⁸ National data on VA patients are abstracted from VA facilities, including patient demographics, medical procedures and diagnoses, hospital visits and vital status.¹⁹ The data files contain information on inpatient stays and outpatient visits and use the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) and Current Procedural Terminology (CPT) systems to code diagnoses and procedures. In addition, the VA Decision Support System (DSS) extracts include pharmacy information and selected laboratory results. To ensure patients were utilizing the VA health system and therefore would have reasonably complete data capture, the study cohort was limited to individuals who had at least one outpatient visit to a VA facility in FY2011. Inclusion criteria were a patient's first hospitalization in FY2011 greater than one day in duration and during which at least two serum creatinine (SCr) values were obtained. Exclusion criteria were: a) pre-existing ESRD or CKD defined by either diagnostic code or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m² in the 365 days before index hospitalization; b) lack of post-hospitalization SCr values; and c) death within one year of index hospitalization. We excluded those who died within 365 days of discharge to focus the analysis on patients developing CKD that would need management for some time in the future rather than in the last year of life. For all analyses, eGFR values were calculated using the CKD-EPI 2009 creatinine equation.²⁰ In the VA system, laboratories began transitioning to serum creatinine measurements with calibration to isotope dilution mass spectrometry reference in 2006 and most facilities had completed this transition by 2010. This study was approved by the VA Ann Arbor Healthcare System institutional review board/human subjects committee (2015–010073) with a waiver of informed consent.

Study Variables and Definitions

Demographic variables included age, gender, and race. Patient comorbidity data (based on ICD-9-CM codes and pharmacy data) was abstracted. Indicators for diabetes mellitus and

hypertension were created and a Charlson comorbidity score was calculated for each patient, excluding diabetes from the score calculation. Additional data included baseline eGFR, baseline urine albumin:creatinine ratio (when available), and clinical details of hospitalization (diagnosis of sepsis, need for mechanical ventilation, length of stay). Baseline SCr (and eGFR) was defined hierarchically from outpatient laboratory results. The mean of SCr values between 7 and 365 days before hospitalization was designated as baseline (88% of cohort).²¹ The 7-day cutoff is arbitrary but was used to avoid selecting an elevated SCr that may have been associated with the need for hospitalization. If the only available outpatient SCr was within 7 days of admission it was used as baseline (9% of cohort), and the first inpatient SCr was used if no outpatient SCr was available (2.6% of cohort).

AKI was defined and staged using the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine-based criteria.¹² Stage 1 AKI was defined as an increase of at least 0.3mg/dl (within 48 hours) but less than twice the baseline creatinine or an increase of 1.5 times baseline (within 7 days); stage 2 AKI is an increase of between 2 and 3 times baseline; and stage 3 AKI is a creatinine increase greater than 3 times baseline or increase to 4.0mg/dl or greater. Patterns of AKI recovery (defined as return of creatinine to <0.3mg/dl above baseline) were examined and organized into the following four categories by pattern of recovery: within 2 days of peak inpatient SCr (fast recovery), between 3 and 10 days from peak (intermediate recovery), those whose SCr was still elevated above baseline at 10 days after peak inpatient SCr (slow or no recovery), and those who did not have follow-up SCr measurements within 10 days of peak inpatient SCr (unknown recovery).

The primary outcome was development of CKD stage 3 or higher by one year following index hospitalization, defined by a physician diagnosis of CKD, dialysis (diagnosis, procedure, or clinic stop code), transplant (diagnosis or procedure), or eGFR <60ml/min/1.73m² on at least two measurements separated by 90 days. Renal function was assessed for SCr values up to 90 days following the one year post-discharge anniversary, but excluded values that were within 90 days following hospital discharge in order to avoid classifying patients with ongoing renal recovery as having established CKD.

Statistical Methods

Modified Poisson regression models using robust (Huber-White, sandwich) standard errors were used to assess the association between AKI recovery pattern (stratified by stage) and subsequent risk for CKD.²² Model covariates were age, race, sex, pre-admission diabetes mellitus and hypertension, diagnosis of sepsis and need for mechanical ventilation during index hospitalization, length of stay, Charlson comorbidity score (from diagnoses in the year prior to and during the index hospitalization), and baseline eGFR. As a sensitivity analysis, we expanded our sample to include patients who were discharged alive but died within one year of their AKI hospitalization and modeled time to CKD (the earliest of first SCr yielding eGFR<60 (which was confirmed by a second measurement at least 90 days later), first diagnosis of CKD, and first indication of dialysis or transplant) using Cox proportional hazards regression, censoring at death. Albuminuria was only available in a subset of

patients and was therefore not included in the primary analysis; however, a subgroup analysis incorporating albuminuria was performed.

Results

Patient Characteristics

During the study period there were 221,087 patients with a hospital stay in the VHA system meeting inclusion criteria. After applying exclusion criteria, the final analysis cohort consisted of 104,764 patient hospitalizations (47% of total). The most common reason for exclusion was pre-existing CKD, accounting for 63% of exclusions (Figure 1). Additional information regarding characteristics of excluded patients is provided in supplemental tables (Table S1 and S2).

Table 1 provides baseline patient characteristics of the analysis cohort overall and stratified by AKI occurrence. Among the final cohort, 17,049 patients (16.3%) had some degree of AKI. AKI patients were older and had slightly lower baseline renal function (eGFR) compared to patients not developing AKI (both $p < 0.001$). Compared to the non-AKI group, a higher proportion of AKI patients were African-American, male, and had pre-existing diabetes and hypertension (all $p < 0.001$).

When examining renal recovery patterns among the AKI patients, the majority (70.8%) experienced fast recovery, 12.2% had intermediate recovery, 11.0% had slow or no recovery, and 6.0% had unknown recovery due to lack of follow-up SCr measurements.

Risk of CKD Development

Approximately one year following the index hospitalization, 19,044 patients (18.2%) had developed CKD stage 3 or higher, including 1.2% with $eGFR < 15$ ml/min/1.73m², dialysis, or transplant. Development of CKD was significantly more common among patients who had AKI during hospitalization than those without AKI (31.8% vs. 15.5%, $p < 0.001$). Table 2 presents the percentage of patients that developed CKD by one year following AKI hospitalization, stratified by both AKI severity and pattern of recovery.

When examining patterns of renal recovery, the risk for development of CKD stage 3 or higher rose progressively with duration of AKI before recovery, and this relationship was consistent across all AKI stages (Table 3). Notably, even fast recovering AKI (within 2 days) remained an independent risk factor for CKD compared to patients without AKI, with a relative risk ranging from 1.43 (95% CI 1.39–1.48) to 1.96 (95% CI 1.64–2.34) for AKI stages 1 and 3 respectively. Patients with unknown recovery had an intermediate relative risk of CKD compared to the more specific renal recovery patterns (RR 1.48 [95% CI 1.34–1.64], 2.08 [95% CI 0.70–6.22] and 2.21 [95% CI 1.17–4.17] for stages 1, 2 and 3 respectively).

Subgroup and Sensitivity Analyses

In the time to CKD model censoring for death, slower AKI recovery remained independently associated with increased risk for development of CKD stage 3 or higher within each stage of AKI, similar to the relationship observed in the modified Poisson

regression models. In patients with stage 1 AKI, the hazard ratios were increased compared to the primary analysis, whereas they were slightly attenuated for patients with stage 2 and 3 AKI (Table 4).

Among the study cohort, 22,646 patients (21.6% of cohort) had available baseline urine albumin measurements. More patients with any abnormal degree of albuminuria (urine albumin:creatinine ratio >30 mg/g; 16.5% of those with urine data) developed AKI compared to those who were tested and had no albuminuria (25.7% vs. 19.1%, $p<0.001$). When incorporating albuminuria into the regression models, compared to no albuminuria the relative risk for CKD among patients with mild albuminuria (30–300mg/g) ranged from 1.11 (95% CI 1.09–1.13) in stage 1 AKI to 1.39 (95% CI 1.30–1.49) in stage 3. For those with moderate-severe albuminuria (>300mg/g), the relative risk ratios were even higher (Table 5). When examining recovery pattern, overall the relative risk for CKD stage 3 or worse remained very similar to that observed in the primary (modified Poisson regression) model. The observation of increasing risk with longer time to recovery remained strong for stage 1 AKI, but was less clear in stage 2 and 3 AKI, possibly related to a loss in power from the more restricted subgroup.

Discussion

AKI has recently emerged as an important and potentially preventable risk factor for CKD.^{8, 23} In this large study of a national sample of U.S. Veterans, we confirmed that AKI was an independent predictor for CKD, with nearly a third of AKI survivors having developed CKD by one year follow-up. Importantly, we found this risk to be present even with the mildest forms of AKI, such as stage 1 AKI with fast recovery, which is often considered clinically benign.

Early studies found an increased risk for CKD and ESRD following an episode of dialysis-requiring AKI,^{4, 24, 25} and subsequent studies have shown a similar association between non-dialysis requiring AKI and later CKD development, even after apparent renal recovery.^{5, 6, 15, 26} However, few studies have included patients with milder forms of AKI, in part due to reliance on administrative data sources which tend to focus on more severe AKI.¹⁴ Using a health system database, Jones and colleagues found that patients with AKI who experienced recovery of renal function to within 10% of baseline creatinine ($n=719$) had nearly six times the odds of developing CKD when compared to propensity-matched non-AKI controls; about a third of patients in this AKI cohort had mild (stage 1) AKI, but results were not reported separately for this group.⁵ Bucaloiu and colleagues examined a regional health center database to identify 1610 patients with *de novo* AKI (defined by at least 50% increase in baseline creatinine) that recovered to within 90% of baseline eGFR by 90 days; these patients had an adjusted HR of 1.91 for development of CKD compared to non-AKI controls.⁶ Our study builds on these findings by putting a focus on mild and rapidly (within 2 days) reversible AKI, which remains associated with significant risk for CKD development. The relative risk of CKD increased with progressively slower rate of renal recovery, irrespective of AKI stage. Our results were robust, and this relationship was preserved across sensitivity and subgroup analyses. These findings highlight rate of renal recovery as an important novel predictor of renal outcomes. Improved awareness among

clinicians of the potential adverse renal outcomes following mild AKI is important as the majority of these patients will not be evaluated by a nephrologist; indeed, hospital chart audits suggest that AKI may not be recognized in many of these patients at all.⁹

Increased awareness may lead to opportunities to improve outcomes following AKI. However, whether or not the relationship between AKI and CKD is causal remains debated.^{27, 28} On the one hand, *in vitro* studies demonstrate a prolonged inflammatory and remodeling response in renal tissues following a transient insult, providing a biologically plausible basis for the transition from AKI to CKD.^{29–31} Furthermore, the results of this study and others show that severity of AKI appears to predict risk for CKD in a dose-dependent manner.^{16, 32, 33} Both observations lend support to a potential causal relationship. Importantly, recent studies in animal models of AKI provide optimism for future therapeutic options to mitigate the risk of CKD following AKI.^{34, 35} On the other hand, mild or transient episodes of AKI in patients with seemingly normal renal function may simply represent an unmasking of subclinical CKD (i.e. decreased renal functional reserve); in this sense, AKI serves as a “failed renal stress test” rather than a causative factor in the development of CKD. In a recent follow-up analysis of a clinical trial comparing on-pump to off-pump cardiopulmonary bypass for patients undergoing coronary artery bypass grafting, despite a significant reduction in AKI events, there was no difference in loss of kidney function at one year.³⁶ Regardless of the nature of the relationship between AKI and CKD, recognition of at-risk patients will allow optimization of preventative strategies such as more aggressive CKD risk factor modification, stricter avoidance of nephrotoxic exposures, and increased renal function monitoring.

Perhaps one of the most surprising findings of this study was the observation that rapidly recovering stage 1 AKI (resolving within 2 days) was associated with a greater than 40% increased risk for CKD compared to non-AKI patients. Such fluctuations in SCr are frequently encountered in the clinical setting and are unlikely to prompt formal involvement of a nephrologist in most cases. Yet our findings are consistent with recent data suggesting that fast recovering, mild AKI in fact may have clinical consequences. Nejat and colleagues demonstrated a release of urinary AKI biomarkers in the setting of clinically determined “pre-renal” AKI, suggesting that injury is occurring and not simply physiologic compensation.³⁷ Similarly, studies in the cardiac literature demonstrate worse long-term survival with even transient AKI compared to no AKI.^{38, 39} Another consideration is that a decrease (or attenuated rise) in SCr can occur due to fluid administration and/or decreased production secondary to inflammation.^{40–42} These effects could result in misclassification of AKI cases as non-AKI cases or suggest earlier recovery than is actually occurring. Despite the inherent limitations to relying on SCr concentrations for AKI diagnosis, it is clear that – irrespective of the underlying pathophysiologic relationship – even rapidly reversible rises in creatinine are associated with increased risk for CKD. Clinicians caring for these patients, the vast majority of whom will be non-nephrologists, need to be aware of the high risk for downstream renal outcomes in this subgroup of AKI patients.

In contrast to prior studies, an important strength of this study was the ability to account for baseline albuminuria in a subset of the study population. As reflected in the KDIGO CKD guidelines, proteinuria is an important risk factor for CKD and CKD progression.⁴³

Proteinuria has also gained recognition as an independent risk factor for AKI,⁴⁴ and thus could be a common element accounting for the association between AKI and CKD. In a population-based study that included 2,234 AKI patients with baseline eGFR ≥ 60 ml/min/1.73m², James and colleagues found that AKI was independently associated with ESRD or a doubling of SCr when accounting for overt (dipstick) proteinuria.⁴⁴ In our analysis, we were able to employ more sensitive definitions of proteinuria (quantitative albuminuria) and CKD (eGFR <60 ml/min/1.73m²) to model CKD risk in a subset of 4586 AKI patients with available urine albumin data. Our results confirm that albuminuria is an independent risk factor for AKI, and this risk increased with higher degrees of albuminuria. While accounting for albuminuria slightly diminished the relative risk of CKD following AKI, overall there remained a strong and independent association between AKI and subsequent CKD risk that increased with slower rate of AKI recovery.

An important limitation of this study is that the VHA database represents a predominantly male population, although our sample contained 5,351 women, 593 of whom experienced AKI. Nevertheless, this database represents one of the only national sources of clinical data, allowing for the study of AKI as defined by consensus criteria; in fact, this study provides an examination of one of the largest cohorts of AKI patients to date. As an observational study, we did not have prescribed follow-up of patients and our results were dependent on availability of follow-up laboratory testing. However, since the VHA is an integrated healthcare system with specific eligibility criteria, we were able to ascertain renal outcomes for the vast majority of patients. We chose to report the primary outcome of CKD as a discrete event by one year follow-up rather than ascertaining a time of onset for CKD because of this heterogeneous laboratory follow-up, making it impossible to pinpoint when a patient developed “incident” CKD. However, when performing time-to-event analysis as a sensitivity analysis, similar results were obtained demonstrating the relationship of increasing CKD risk with longer recovery time from AKI.

This study demonstrates the significant risk for CKD development following an episode of AKI. This risk increases with worsening severity of AKI, as defined by duration of injury and time to recovery, and was present with even the mildest forms of AKI with fast recovery. These results should raise awareness to the potential long-term development of CKD following AKI, the majority of which will continue to be managed by non-nephrologists. Our results support the need for regular follow-up of patients in the period following discharge from the hospital for earlier detection of CKD development, even among those with mild AKI that may have recovered during the hospital stay. Improved recognition of patients at risk for CKD development will facilitate optimal use of preventive measures and risk factor modification. Additional research is also needed to identify approaches to mitigate the risk of transition from AKI to CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Selection of study cohort.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; d, day(s); ESRD, end-stage renal disease; SCr, serum creatinine.

AKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to <0.3mg/dl above baseline as 2 days; 3 to 10 days; SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.

Table 1:

Patient characteristics, overall and by presence of AKI during index hospitalization

Variable	Total (n=104,764, 100%)		No AKI (n=87,715, 83.7%)		With AKI (n=17,049, 16.3%)		p-value
	N	% or Mean (SD)	N	% or Mean (SD)	N	% or Mean (SD)	
Baseline eGFR, mean (SD) (mL/min/1.73m ²)	104,764	86.7 (15.5)	87,715	87.2 (14.4)	17,049	83.9 (15.5)	<0.001
Number of outpatient SCr, year before admission, mean (SD)	104,764	3.5 (3.4)	87,715	3.4 (3.4)	17,049	3.7 (3.5)	<0.001
Age (years), mean (SD)	104,764	61.8 (11.8)	87,715	61.6 (11.9)	17,049	63.1 (10.8)	<0.001
20 to <30 years, %	1,544	1.5	1,423	1.6	121	0.7	<0.001
30 to <40 years, %	2,885	2.8	2,588	3.0	297	1.7	<0.001
40 to <50 years, %	8,806	8.4	7,702	8.8	1,104	6.5	<0.001
50 to <60 years, %	27,960	26.7	23,572	26.9	4,388	25.7	0.002
60 to <70 years, %	42,476	40.5	35,026	39.9	7,450	43.7	<0.001
70+ years, %	21,093	20.1	17,404	19.8	3,689	21.6	<0.001
Race and ethnicity, %							
Non-Hispanic white	72,226	68.9	61,175	69.7	11,051	64.8	<0.001
Non-Hispanic African American	20,096	19.2	15,991	18.2	4,105	24.1	<0.001
American Indian/Alaska Native	581	0.6	497	0.6	84	0.5	0.2
Pacific Islander/Native Hawaiian	578	0.6	493	0.6	85	0.5	0.3
Hispanic	4,258	4.1	3,594	4.1	664	3.9	0.2
Asian	230	0.2	198	0.2	32	0.2	0.3
Other/Unknown	6,795	6.5	5,767	6.6	1,028	6.0	0.008
Female, %	5,351	5.1	4,758	5.4	593	3.5	<0.001
Pre-admission diabetes, % ^a	37,361	35.7	29,448	33.6	7,913	46.4	<0.001
Pre-admission hypertension, % ^b	80,655	77.0	66,024	75.3	14,631	85.8	<0.001
Sepsis diagnosis, %	249	0.2	66	0.1	183	1.1	<0.001
Mechanical ventilation, %	1,922	1.8	1,022	1.2	900	5.3	<0.001
Surgical DRG, %	26,947	25.7	22,307	25.4	4,640	27.2	<0.001
Length of stay, days	104,764	7.6 (23.6)	87,715	7.3 (24.8)	17,049	9.2 (15.9)	<0.001
2 – 3 days, %	42,416	40.5	37,180	42.4	5,236	30.7	<0.001
4 – 6 days, %	31,263	29.8	26,599	30.3	4,664	27.4	<0.001
7 – 14 days, %	15,951	15.2	12,344	14.1	3,607	21.2	<0.001
15 – 21 days, %	4,276	4.1	3,094	3.5	1,182	6.9	<0.001
22 – 30 days, %	1,959	1.9	1,402	1.6	557	3.3	<0.001
31 or more days, %	2,690	2.6	2,014	2.3	676	4.0	<0.001
Had baseline urine albumin, %	22,646	21.6	18,060	20.6	4,586	26.9	<0.001
Charlson comorbidity score, mean (SD) ^c	104,764	1.21 (1.4)	87,715	1.2 (1.4)	17,049	1.3 (1.4)	<0.001
0, %	40,488	38.6	34,520	39.4	5,968	35.0	
1, %	29,443	28.1	24,531	28.0	4,912	28.8	
2, %	18,432	17.6	15,187	17.3	3,245	19.0	<0.001
3, %	9,941	9.5	8,224	9.4	1,717	10.1	

Variable	Total (n=104,764, 100%)		No AKI (n=87,715, 83.7%)		With AKI (n=17,049, 16.3%)		p-value
	N	% or Mean (SD)	N	% or Mean (SD)	N	% or Mean (SD)	
4, %	3,558	3.4	2,881	3.3	677	4.0	
5 or more, %	2,902	2.8	2,372	2.7	530	3.1	
Charlson conditions, %							
Acute myocardial infarction	4,298	4.1	3,497	4.0	801	4.7	<0.001
Past acute MI	5,258	5.0	4,408	5.0	850	5.0	0.8
Heart failure	14,039	13.4	10,957	12.5	3,082	18.1	<0.001
Peripheral vascular disease (Dx)	12,608	12.0	10,215	11.6	2,393	14.0	<0.001
Peripheral vascular disease (No Dx but has CPT)	1,521	1.5	1,218	1.4	303	1.8	<0.001
Cerebrovascular disease	13,896	13.3	11,594	13.2	2,302	13.5	0.3
Lung disease	35,248	33.6	29,507	33.6	5,741	33.7	0.9
Dementia	1,067	1.0	887	1.0	180	1.1	0.6
Paralysis	2,091	2.0	1,747	2.0	344	2.0	0.8
Diabetes, no sequelae (Dx only) ^d	35,439	33.8	27,816	31.7	7,623	44.7	<0.001
Diabetes with sequelae (Dx only) ^d	12,505	11.9	9,546	10.9	2,959	17.4	<0.001
Mild liver disease	4,236	4.0	3,459	3.9	777	4.6	<0.001
Moderate/severe liver disease	1,944	1.9	1,556	1.8	388	2.3	<0.001
Ulcer, without perforation	2,907	2.8	2,428	2.8	479	2.8	0.8
Ulcer with perforation	594	0.6	477	0.5	117	0.7	0.03
Rheumatoid/autoimmune	2,147	2.0	1,787	2.0	360	2.1	0.5
AIDS	1,353	1.3	1,109	1.3	244	1.4	0.08
Metastatic cancer	2,382	2.3	1,998	2.3	384	2.3	0.8
Non-metastatic cancer	18,387	17.6	15,153	17.3	3,234	19.0	<0.001
HIV, not AIDS	572	0.5	493	0.6	79	0.5	0.1
Number of outpatient SCr, year after discharge, mean (SD)	104,764	5.1 (5.9)	87,715	5.0 (5.7)	17,049	5.7 (7.0)	<0.001
AKI by severity, % ^e							
No AKI	87,715	83.7	87,715	100.0	-	0.0	
Stage 1	15,566	14.9	-	-	15,566	91.3	
Stage 2	561	0.5	-	-	561	3.3	
Stage 3	922	0.9	-	-	922	5.4	
AKI by recovery pattern, % ^f							
No AKI	87,715	83.7	87,715	100.0	-	0.0	
2 days	12,072	11.5	-	-	12,072	70.8	
3 to 10 days	2,072	2.0	-	-	2,072	12.2	
Still elevated after 10 days	1,874	1.8	-	-	1,874	11.0	
No SCr measurement within 10 days	1,031	1.0	-	-	1,031	6.0	

Sample includes patients who survived 365 days following discharge from index admission.

Abbreviations: AIDS, acquired immune deficiency syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CPT, current procedural terminology; DRG, diagnosis related group; Dx, diagnosis code; eGFR, estimated glomerular filtration rate (using CKD-Epidemiology

Collaboration equation); HIV, human immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes; MI, myocardial infarction; SCr, serum creatinine; SD, standard deviation.

^aPre-admission diabetes mellitus is defined by the presence of a diagnosis code, hemoglobin A1c > 6.5, serum glucose > 200, or prescription of a diabetes medication in the 365 days before index admission.

^bPre-admission hypertension is defined by the presence of a diagnosis code or prescription for an antihypertensive medication in the 365 days before the index admission.

^cCharlson comorbidity score excludes diabetes mellitus and chronic kidney disease but includes cancer, HIV and AIDS.

^dCondition not included in Charlson score due to separate inclusion in models.

^eAKI severity is defined by KDIGO criteria: Stage 1 is an increase in inpatient SCr of 0.3mg/dl but less than twice baseline creatinine (or an increase of 1.5 times baseline even if less than 0.3mg/dl); Stage 2 is an increase between 2 and 3 times baseline; and Stage 3 is an increase greater than 3 times baseline or an increase to 4.0mg/dl or greater. Conversion factors for units: SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

^fAKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to <0.3mg/dl above baseline as 2 days; 3 to 10 days; SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.

Table 2:

Development of Stage 3 and higher CKD and Stage 5 or ESRD by one year following index hospitalization discharge, stratified by AKI stage and recovery pattern

	Total (N)	Stage 3 or higher CKD by one year ^a Events (N)	Percent of total	Stage 5 CKD/ESRD by one year ^b Events (N)	Percent of total
Overall total	104,764	19,044	18.2	1,271	1.2
No AKI	87,715	13,625	15.5	1,044	1.2
Any AKI	17,049	5,419	31.8	227	1.3
AKI by severity ^c					
Stage 1	15,566	4,774	30.7	191	1.2
Stage 2	561	206	26.7	7	1.3
Stage 3	922	439	47.6	29	3.2
AKI by recovery pattern ^d					
2 days	12,072	3,341	27.7	127	1.1
3 to 10 days	2,072	823	39.7	36	1.7
Still elevated after 10 days	1,874	997	53.2	48	2.6
No SCr measurement within 10 days	1,031	258	25.0	16	1.6

Differences for AKI yes v. no, AKI by severity categories, and AKI by recovery patterns for each outcome variable are statistically significant at the $p < 0.001$ level. Sample includes only patients who survived 365 days following discharge from index admission.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (using CKD-Epidemiology Collaboration equation); ESRD, end-stage renal disease; KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine.

^a“Stage 3 or higher CKD by one year” is the presence of a physician diagnosis of CKD, an indication of dialysis post discharge (diagnosis, procedure, or clinic stop code) or transplant (diagnosis) or 2 follow-up SCr results at least 90 days apart, both yielding $eGFR < 60 \text{ mL/min/1.73m}^2$. Follow-up SCr lab results were between 90 days post discharge and 90 days after one-year discharge anniversary.

^b“Stage 5 CKD/ESRD by one year” is an indication of dialysis or transplant or a follow-up SCr yielding $eGFR < 15 \text{ mL/min/1.73m}^2$. Because of incomplete capture of dialysis and transplant care received by VA patients outside of the VA health system in the study data, some Stage 5 CKD patients may actually be ESRD and receiving dialysis outside of the VA health system.

^cAKI severity is defined by KDIGO criteria: Stage 1 is an increase in inpatient SCr of 0.3mg/dL but less than twice baseline SCr (or an increase of 1.5 times baseline even if less than 0.3mg/dL); Stage 2 is an increase between 2 and 3 times baseline; and Stage 3 is an increase greater than 3 times baseline or an increase to 4.0mg/dL or greater. Conversion factors for units: SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

^dAKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to $< 0.3\text{mg/dL}$ above baseline as < 2 days; 3 to 10 days; SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.

Table 3:

Adjusted relative risk ratios for the development of Stage 3 or higher CKD^a by one year post-discharge from the index hospitalization, stratified by AKI stage^b

	Stage 1 AKI				Stage 2 AKI				Stage 3 AKI			
	RR	95% CI	p		RR	95% CI	p		RR	95% CI	p	
AKI recovery pattern ^b												
No AKI	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
2 days	1.43	1.39	1.48	<0.001	1.80	1.46	2.23	<0.001	1.96	1.64	2.34	<0.001
3 to 10 days	2.00	1.88	2.12	<0.001	1.91	1.49	2.45	<0.001	2.20	1.91	2.53	<0.001
Still elevated after 10 days	2.65	2.51	2.80	<0.001	3.31	2.85	3.84	<0.001	3.59	3.27	3.94	<0.001
No SCr measurement within 10 days	1.48	1.34	1.64	<0.001	2.08	0.70	6.22	0.2	2.21	1.17	4.17	0.01
Baseline eGFR, per 10 ml/min/m ²	0.71	0.70	0.71	<0.001	0.70	0.69	0.70	<0.001	0.70	0.69	0.71	<0.001
Age at admission, years												
20 to 29	0.81	0.65	1.03	0.08	0.85	0.66	1.09	0.2	0.83	0.64	1.06	0.1
30 to 39	0.90	0.78	1.03	0.1	0.84	0.72	0.99	0.04	0.84	0.72	0.98	0.03
40 to 49	0.99	0.93	1.06	0.8	0.98	0.91	1.06	0.6	0.98	0.91	1.06	0.6
50 to 59	1.00	0.96	1.04	0.9	0.98	0.94	1.03	0.5	0.98	0.94	1.03	0.4
60 to 69	0.96	0.94	0.99	0.01	0.96	0.92	0.99	0.01	0.96	0.92	0.99	0.01
70 or older	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Race and ethnicity												
Non-Hispanic white	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Non-Hispanic black	1.30	1.26	1.34	<0.001	1.32	1.28	1.37	<0.001	1.31	1.26	1.36	<0.001
Hispanic	1.00	0.83	1.20	0.9	1.02	0.83	1.27	0.8	1.04	0.85	1.28	0.7
Asian	1.00	0.84	1.18	0.9	1.01	0.83	1.23	0.9	0.98	0.80	1.20	0.8
American Indian/Alaska native	1.03	0.96	1.10	0.4	1.05	0.97	1.14	0.2	1.04	0.96	1.13	0.3
Pacific Islander/Native Hawaiian	1.15	0.88	1.50	0.3	1.11	0.81	1.53	0.5	1.10	0.80	1.51	0.6
Unknown	0.90	0.85	0.95	<0.001	0.91	0.85	0.97	0.003	0.91	0.85	0.97	0.004
Female sex	0.80	0.75	0.87	<0.001	0.77	0.71	0.84	<0.001	0.78	0.71	0.84	<0.001
Pre-admission diabetes mellitus ^c	1.35	1.31	1.38	<0.001	1.38	1.34	1.42	<0.001	1.37	1.33	1.42	<0.001
Pre-admission hypertension ^d	1.13	1.08	1.17	<0.001	1.11	1.06	1.16	<0.001	1.11	1.06	1.16	<0.001
Length of stay												
2 – 3 days	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
4 – 6 days	1.04	1.01	1.07	0.004	1.05	1.02	1.09	0.004	1.05	1.01	1.08	0.01
7 – 14 days	1.08	1.04	1.11	<0.001	1.13	1.08	1.17	<0.001	1.12	1.07	1.17	<0.001
15 – 21 days	1.04	0.98	1.11	0.2	1.10	1.01	1.19	0.02	1.11	1.03	1.20	0.01
22 – 30 days	1.12	1.02	1.22	0.01	1.11	0.99	1.25	0.07	1.12	0.99	1.25	0.06
31 or more days	1.06	0.97	1.15	0.2	1.01	0.90	1.13	0.9	1.03	0.92	1.15	0.6
Sepsis diagnosis during this hospitalization	1.21	0.96	1.52	0.1	1.46	1.03	2.07	0.03	1.13	0.83	1.55	0.4
Mechanical ventilation this hospitalization	1.01	0.93	1.10	0.8	0.97	0.85	1.11	0.7	0.99	0.87	1.13	0.9
Charlson comorbidity score ^e , per unit	1.13	1.12	1.14	<0.001	1.14	1.13	1.15	<0.001	1.14	1.13	1.15	<0.001

All variables included in the models are shown in table. Separate modified Poisson regression models estimated for each stage of AKI compared to no AKI among patients who survived 365 days following discharge from index admission.

Abbreviations: AIDS, acquired immune deficiency syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CI, 95% confidence interval; eGFR, estimated glomerular filtration rate (using CKD-Epidemiology Collaboration equation); HIV, human immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes; p, p-value; ref, reference group; RR, relative risk ratio; SCr, serum creatinine.

^a“Stage 3 or higher CKD by one year” is the presence of a physician diagnosis of CKD, an indication of dialysis post discharge (diagnosis, procedure, or clinic stop code) or transplant (diagnosis) or 2 follow-up SCr results at least 90 days apart, both yielding eGFR < 60 mL/min/1.73m². Follow-up SCr lab results were between 90 days post discharge and 90 days after one-year discharge anniversary.

^b AKI severity is defined by KDIGO criteria: Stage 1 is an increase in inpatient SCr of 0.3mg/dl but less than twice baseline SCr (or an increase of 1.5 times baseline even if less than 0.3mg/dl); Stage 2 is an increase between 2 and 3 times baseline; and Stage 3 is an increase greater than 3 times baseline or an increase to 4.0mg/dl or greater. Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4.

^b AKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to <0.3mg/dl above baseline as < 2 days; 3 to 10 days; and SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.

^cPre-admission diabetes mellitus is defined by the presence of a diagnosis code, hemoglobin A1c > 6.5, serum glucose > 200, or prescription of a diabetes medication in the 365 days before index admission.

^dPre-admission hypertension is defined by the presence of a diagnosis code or prescription for an antihypertensive medication in the 365 days before the index admission.

^eCharlson comorbidity score excludes diabetes mellitus and chronic kidney disease but includes cancer, HIV and AIDS.

Table 4:

Adjusted hazard ratios for the effect of AKI recovery pattern on death-censored time to development of Stage 3 or higher CKD by one year after discharge from the index hospitalization, stratified by AKI stage^a

	Stage 1 AKI				Stage 2 AKI				Stage 3 AKI			
	HR	95% CI		p	HR	95% CI		p	HR	95%CI		p
AKI by recovery pattern ^b												
No AKI	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
2 days	1.49	1.43	1.54	<0.001	1.32	1.01	1.72	0.04	1.52	1.23	1.89	<0.001
3 to 10 days	2.32	2.16	2.49	<0.001	1.66	1.24	2.23	0.001	1.61	1.31	1.97	<0.001
Still elevated after 10 days	3.25	3.02	3.50	<0.001	3.81	3.09	4.68	<0.001	2.97	2.55	3.46	<0.001
No SCr measures in 10 days	1.78	1.60	2.00	<0.001	2.28	0.57	9.13	0.2	2.01	1.00	4.03	0.05

Abbreviations: AIDS, acquired immune deficiency syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CI, 95% confidence interval; eGFR, estimated glomerular filtration rate (using CKD-Epidemiology Collaboration equation); HIV, human immunodeficiency virus; HR, hazard ratio; KDIGO, Kidney Disease Improving Global Outcomes; p, p-value; ref, reference group; SCr, serum creatinine.

This analysis included all patients discharged alive from the index hospitalization (n=121,123). Separate Cox proportional hazards regression models were used to model time to the development of Stage 3 or higher CKD [defined as the earliest of first physician diagnosis of CKD, indication of dialysis (diagnosis, procedure, or clinic stop code), transplant (diagnosis), or the first of two follow-up SCr results yielding eGFR < 60 mL/min/1.73m² at least 90 days apart] for each stage of AKI compared to no AKI. Follow-up started at day of discharge.

Each model also included baseline eGFR, age, race, sex, pre-admission diabetes mellitus (defined by the presence of a diagnosis code, hemoglobin A1c > 6.5, serum glucose > 200, or prescription of a diabetes medication in the 365 days before index admission), pre-admission hypertension (defined by the presence of a diagnosis code or prescription for an antihypertensive medication in the 365 days before the index admission), sepsis diagnosis, mechanical ventilation, and length of stay during index admission, and Charlson comorbidity scores, excluding diabetes mellitus and CKD and including cancer, HIV and AIDS.

^aAKI stage is defined by KDIGO criteria: Stage 1 is an increase in inpatient SCr of 0.3mg/dl but less than twice baseline SCr (or an increase of 1.5 times baseline even if less than 0.3mg/dl); Stage 2 is an increase between 2 and 3 times baseline; and Stage 3 is an increase greater than 3 times baseline or an increase to 4.0mg/dl or greater. Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4.

^bAKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to <0.3mg/dl above baseline as < 2 days; 3 to 10 days; and SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.

Table 5:

Adjusted relative risk ratios for the effect of AKI recovery pattern and baseline albuminuria on the development of Stage 3 or higher CKD by one year after discharge from the index hospitalization, among those with baseline albuminuria measurement, stratified by AKI stage^a

	Stage 1 AKI				Stage 2 AKI				Stage 3 AKI			
	RR	95% CI		p	RR	95% CI		p	RR	95%CI		p
AKI by recovery pattern ^b												
No AKI	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
2 days	1.40	1.32	1.48	<0.001	1.85	1.30	2.64	<0.001	1.80	1.33	2.45	<0.001
3 to 10 days	2.05	1.86	2.27	<0.001	1.58	1.02	2.44	0.04	1.83	1.41	2.37	<0.001
Still elevated after 10 days	2.33	2.10	2.59	<0.001	3.00	2.32	3.88	<0.001	3.48	2.96	4.10	<0.001
No SCr measures in 10 days	--	--	--	--	--	--	--	--	--	--	--	--
Baseline albuminuria												
0 to <30	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
30 to 300	1.11	1.09	1.13	<0.001	1.40	1.30	1.50	<0.001	1.39	1.30	1.49	<0.001
>300	1.35	1.28	1.43	<0.001	1.71	1.50	1.95	<0.001	1.72	1.51	1.95	<0.001

Abbreviations: AIDS, acquired immune deficiency syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; CI, 95% confidence interval; eGFR, estimated glomerular filtration rate (using CKD-Epidemiology Collaboration equation); HIV, human immunodeficiency virus; KDIGO, Kidney Disease Improving Global Outcomes; p, p-value; ref, reference group; RR, relative risk ratio; SCr, serum creatinine.

This analysis included all patients who survived 365 days following discharge from index hospitalization who had at least one outpatient measure of urine albumin in the 365 days before the index admission. Because there were too few observations with no SCr measures within the 10 days following inpatient SCr peak to estimate relative risk ratios, these observations were excluded (final sample size=22,432). Separate modified Poisson regression models were used to model the development of Stage 3 or higher CKD [physician diagnosis of CKD, indication of dialysis (diagnosis, procedure, or clinic stop code), transplant (diagnosis) or two follow-up SCr results yielding eGFR < 60 mL/min/1.73m² at least 90 days apart] for each stage of AKI compared to no AKI.

Each model also included baseline eGFR, age, race, sex, pre-admission diabetes mellitus (defined by the presence of a diagnosis code, hemoglobin A1c > 6.5, serum glucose > 200, or prescription of a diabetes medication in the 365 days before index admission), pre-admission hypertension (defined by the presence of a diagnosis code or prescription for an antihypertensive medication in the 365 days before the index admission), sepsis diagnosis, mechanical ventilation, and length of stay during index admission, and Charlson comorbidity scores, excluding diabetes mellitus and CKD and including cancer, HIV and AIDS.

^aAKI stage is defined by KDIGO criteria: Stage 1 is an increase in inpatient SCr of 0.3mg/dl but less than twice baseline SCr (or an increase of 1.5 times baseline even if less than 0.3mg/dl); Stage 2 is an increase between 2 and 3 times baseline; and Stage 3 is an increase greater than 3 times baseline or an increase to 4.0mg/dl or greater. Conversion factors for units: SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

^bAKI recovery classified by the number of days between peak inpatient SCr and the return of SCr to <0.3mg/dl above baseline as < 2 days; 3 to 10 days; and SCr still elevated at 10 days following peak; and no SCr measurement found between peak and 10 days following peak. Both inpatient and outpatient SCr results were used when patients were discharged prior to 10 days following peak.