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Original Investigation

Acute Kidney Injury Recovery Pattern and Subsequent Risk of CKD: An Analysis of Veterans Health Administration Data

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

Study Design: Retrospective cohort.

Setting & Participants: Patients in the Veterans Health Administration in 2011 hospitalized (>24 hours) with at least 2 inpatient serum creatinine measurements, baseline estimated glomerular filtration rate > 60 mL/min/1.73 m^2, and no diagnosis of end-stage renal disease or non−dialysis-dependent CKD: 17,049 (16.3%) with and 87,715 without AKI.

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

Outcome: CKD stage 3 or higher, defined as 2 outpatient estimated glomerular filtration rates < 60 mL/min/1.73 m^2 at least 90 days apart or CKD diagnosis, dialysis therapy, or transplantation.

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

Results: Most patients' AKI episodes were stage 1 (91%) and 71% recovered within 2 days. At 1 year, 18.2% had developed CKD (AKI, 31.8%; non-AKI, 15.5%; $P < 0.001$). In stage 1, the adjusted relative risk ratios for CKD stage 3 or higher were 1.43 (95% CI, 1.39-1.48), 2.00 (95% CI, 1.88-2.12), and 2.65 (95% CI, 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 the development of CKD by 1 year following hospitalization and timing of AKI recovery is a strong predictor, even for the mildest forms of AKI.

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INDEX WORDS: Renal recovery; acute kidney injury (AKI); AKI outcomes; chronic kidney disease (CKD); acute on chronic kidney disease; kidney function; serum creatinine; renal complications; recovery speed; Veterans Administration (VA).

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

Although 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

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kidney function.[8] However, 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 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; one of the objectives of Healthy People 2020 is to increase the proportion of patients with AKI 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 toward 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 US Veterans Health Administration (VHA)/Department of Veterans Affairs (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 for adverse kidney disease outcomes following hospitalization for AKI in patients without preexisting 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 (October through September) 2010 to 2012 was used for the study. The VHA is the largest integrated health care system in the United States.[18] National data for VA patients are abstracted from VA facilities, including patient demographics, medical procedures and diagnoses, hospital visits, and vital status.[19] Data files contain information for inpatient stays and outpatient visits and use the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) and *Current Procedural Terminology* systems to code diagnoses and procedures. In addition, the VA Decision Support System extracts include pharmacy information and selected laboratory results. To ensure that patients were using the VA health system and therefore would have reasonably complete data capture, the study cohort was limited to individuals who had at least 1 outpatient visit to a VA facility in fiscal year 2011. Inclusion criteria were a patient's first hospitalization in fiscal year 2011 longer than 1 day in duration and during which at least 2 serum creatinine (Scr) values were obtained. Exclusion criteria were as follows: (1) preexisting ESRD or non−dialysis-dependent CKD defined by either diagnostic code or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 in the 365 days before the index hospitalization, (2) lack of posthospitalization Scr values, and (3) death within 1 year of the index hospitalization. We excluded those who died within 365 days of discharge to focus the analysis on patients developing CKD who would need management for some time in the future rather than in the last year of life. For all analyses, eGFRs were calculated using the CKD-EPI (CKD Epidemiology Collaboration) 2009 creatinine equation.[20] In the VA system, laboratories began transitioning to Scr 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, sex, and race. Patient comorbid condition data (based on *ICD-9-CM* codes and pharmacy data) were 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, and length of stay). Baseline Scr (and eGFR) was defined hierarchically from outpatient laboratory results. The mean of Scr values 7 to 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 level that may have been associated with the need for hospitalization. If the only available outpatient Scr level was within 7 days of admission, it was used as baseline (9% of cohort), and the first inpatient Scr level was used if no outpatient Scr level was available (2.6% of cohort).

AKI was defined and staged using KDIGO (Kidney Disease: Improving Global Outcomes) creatinine-based criteria.[12] Stage 1 AKI was defined as an Scr level increase ≥ 0.3 mg/dL (within 48 hours) but less than twice the baseline Scr or an increase of 1.5 times baseline (within 7 days), stage 2 AKI is an increase of 2 to 3 times baseline, and stage 3 AKI is an Scr level increase greater than 3 times baseline or an increase to $\geq$4.0 mg/dL. Patterns of AKI recovery (defined as return of Scr to $<$0.3 mg/dL above baseline) were examined and organized into the following 4 categories by pattern of recovery: within 2 days of peak inpatient Scr level (fast recovery), in 3 to 10 days from peak (intermediate recovery), Scr level 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 the development of CKD stage 3 or higher by 1 year following the index hospitalization, defined by a physician diagnosis of CKD, dialysis (diagnosis, procedure, or clinic stop code), transplantation (diagnosis or procedure), or eGFR < 60 mL/min/1.73 m^2 on at least 2 measurements separated by 90 days. Kidney function was assessed for Scr values up to 90 days following the 1-year postdischarge 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, preadmission