Acute Kidney Injury and Risk of Incident Heart Failure Among US Veterans

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Background: Acute kidney injury (AKI) is common and associated with poor outcomes. Heart failure is a leading cause of cardiovascular disease among patients with chronic kidney disease. The relationship between AKI and heart failure remains unknown and may identify a novel mechanistic link between kidney and cardiovascular disease.

Study Design: Observational study.

Setting & Participants: We studied a national cohort of 300,868 hospitalized US veterans (2004-2011) without a history of heart failure.

Predictor: AKI was the predictor and was defined as a 0.3-mg/dL or 50% increase in serum creatinine concentration from baseline to the peak hospital value. Patients with and without AKI were matched (1:1) on 28 in- and outpatient covariates using optimal Mahalanobis distance matching.

Outcomes: Incident heart failure was defined as 1 or more hospitalization or 2 or more outpatient visits with a diagnosis of heart failure within 2 years through 2013.

Results: There were 150,434 matched pairs in the study. Patients with and without AKI during the index hospitalization were well matched, with a median preadmission estimated glomerular filtration rate of 69 mL/min/1.73 m^2. The overall incidence rate of heart failure was 27.8 (95% CI, 19.3-39.9) per 1,000 person-years. The incidence rate was higher in those with compared with those without AKI: 30.8 (95% CI, 21.8-43.5) and 24.9 (95% CI, 16.9-36.5) per 1,000 person-years, respectively. In multivariable models, AKI was associated with 23% increased risk for incident heart failure (HR, 1.23; 95% CI, 1.19-1.27).

Limitations: Study population was primarily men, reflecting patients seen at Veterans Affairs hospitals.

Conclusions: AKI is an independent risk factor for incident heart failure. Future studies to identify underlying mechanisms and modifiable risk factors are needed.

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The incidence of acute kidney injury (AKI) is increasing in the US population.[1,2] AKI is strongly linked to poor long-term outcomes, including the development of chronic kidney disease (CKD) and death.[3,4] AKI may also be associated with subsequent atherosclerotic cardiovascular disease.[5-8]

Among patients with CKD, heart failure is a common manifestation of cardiovascular disease. The risk for incident heart failure is 3-fold greater in patients with CKD compared with those without CKD.[9] The mechanisms linking kidney disease and heart failure are multifactorial and include disturbances in sodium handling, sympathetic stimulation, inflammation, upregulation of the renin-angiotensin-aldosterone system (RAAS), and alterations of mineral metabolism.[10-15] Many of these same biological alterations may also exist or become accelerated in the setting of AKI.[16]

It remains unknown whether AKI is also associated with subsequent incident heart failure. One prior study of 2,000 patients hospitalized with acute ST-elevation myocardial infarction reported that those with AKI had increased risk for subsequent heart failure hospitalization (a secondary end point in the analysis).[17] However, this study focused on a specific high-risk population with known cardiovascular disease, who may have a differential risk for heart failure. Understanding the long-term risk for incident heart failure in patients who experience AKI may guide appropriate therapies and follow-up. In this study, we examined the association of AKI with incident heart failure in a national cohort of US veterans.

Methods

Study Setting and Design

A national retrospective cohort of 6,390,410 patient hospitalizations was collected including all adult admissions in 116 Veterans Affairs (VA) hospitals from January 1, 2002, through December 31, 2013. The VA uses an electronic health record, Computerized Patient Record System, in place since the 1990s,[18,19] with nationally reliable data for the domains required for this study since 2002.[19] For this analysis, we included 4,970,665 patients 18 years or older who had qualifying hospitalizations after January 1, 2004, through December 31, 2011, to allow 2 years of data collection before the index hospitalization to define baseline covariates and allow 2 years of follow-up time after the index hospitalization (Fig 1).

This study was approved by the Institutional Review Board and the Research and Development Committee of the VA Tennessee Valley Healthcare System. The requirement

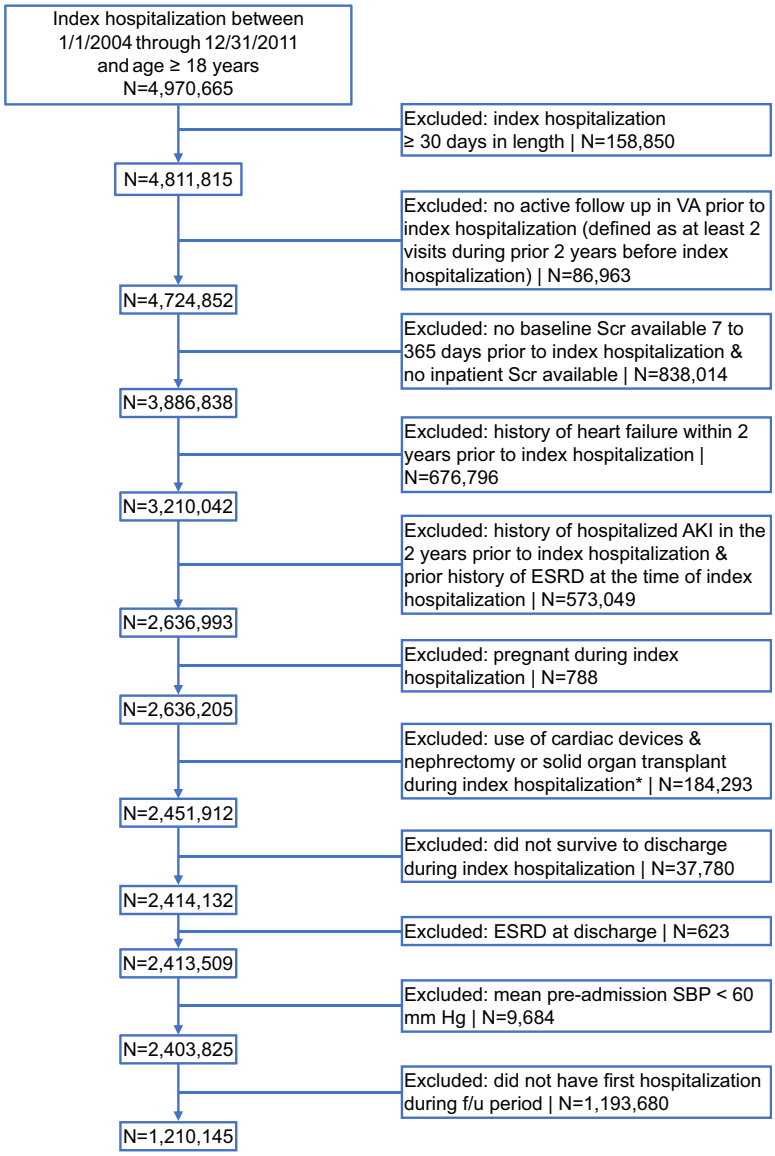

Figure 1. Derivation of the study population. *Intra-aortic balloon pump, ventricular assist device, or extracorporeal membrane oxygenation. Abbreviations: AKI, acute kidney injury; ESRD, end-stage renal disease; f/u, follow-up; SBP, systolic blood pressure; Scr, serum creatinine; VA, Veterans Affairs.

for informed consent was waived due to the use of deidentified data.

Cohort Exclusion Criteria

This analysis only included qualifying patients who had AKI and covariate matched patients who did not have AKI (non-AKI) during the index hospitalization. A summary of patient hospitalization exclusions is shown in Fig 1. For those with multiple hospitalizations, we selected the first qualifying hospitalization. We excluded patients with preexisting heart failure within 2 years of the index hospitalization. Following the exclusions, 1,210,145 hospitalizations remained eligible for the study.

Data Collection

All data were collected during the study period from the VA national Corporate Data Warehouse, which aggregates data from each VA facility's electronic health record.[18,20] All VA laboratory data from out- and inpatient encounters were obtained for each patient. Diagnoses were obtained from the *International Classification of Diseases, Ninth Revision* (*ICD-9*), *ICD-9* Procedure, and *Current Procedural Terminology* (*CPT*) codes. Medications were obtained from preadmission medication lists and medication administration structured data. Radiologic studies such as computed tomography were recorded from orders placed in the Computerized Patient Record System. The time frame we collected data was from 2 years before the index hospitalization for AKI (−730 days to −1 day before admission).

Study Definition of AKI

The first AKI event during the index hospitalization was our primary exposure. AKI was determined using creatinine laboratory value data and dialysis procedure codes collected during the index hospitalization. We defined the primary predictor as AKI of any stage based on the KDIGO (Kidney Disease: Improving Global Outcomes) creatinine-based staging criteria.[21] We examined severity of AKI as an