Acute kidney injury is a risk factor for subsequent proteinuria

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Acute kidney injury (AKI) is associated with subsequent chronic kidney disease (CKD), but the mechanism is unclear. To clarify this, we examined the association of AKI and new-onset or worsening proteinuria during the 12 months following hospitalization in a national retrospective cohort of United States Veterans hospitalized between 2004-2012. Patients with and without AKI were matched using baseline demographics, comorbidities, proteinuria, estimated glomerular filtration rate, blood pressure, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ACEI/ARB) use, and inpatient exposures linked to AKI. The distribution of proteinuria over one year post-discharge in the matched cohort was compared using inverse probability sampling weights. Subgroup analyses were based on diabetes, pre-admission ACEI/ARB use, and AKI severity. Among the 90,614 matched AKI and non-AKI pairs, the median estimated glomerular filtration rate was 62 mL/min/1.73m^2. The prevalence of diabetes and hypertension were 48% and 78%, respectively. The odds of having one plus or greater dipstick proteinuria was significantly higher during each month of follow-up in patients with AKI than in patients without AKI (odds ratio range 1.20-1.39). Odds were higher in patients with Stage II or III AKI (odds ratios 1.32-1.81) than in Stage I AKI (odds ratios 1.18-1.32), using non-AKI as the reference group. Results were consistent regardless of diabetes status or baseline ACEI/ARB use. Thus, AKI is a risk factor for incident or worsening proteinuria, suggesting a possible mechanism linking AKI and future CKD. The type of proteinuria, physiology, and clinical significance warrant further study as a potentially modifiable risk factor in the pathway from AKI to CKD.

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Acute kidney injury (AKI) increasingly is recognized as a common complication of acute illness and as a risk factor for morbidity and mortality.[1–10] AKI is associated with the development or progression of chronic kidney disease (CKD), but the mechanisms are not well understood.[11–18] Proteinuria is also a well-established predictor of future loss of kidney function,[19–22] and better understanding of the longitudinal association between AKI and proteinuria may help reveal a mechanism linking AKI and progression of CKD.

Preclinical data demonstrate that animals subjected to renal ischemia-reperfusion injury develop proteinuria even after serum creatinine level has returned to baseline.[23] Prior studies in children have shown an increased risk of developing proteinuria and CKD after AKI, but these studies were limited by a lack of appropriate controls and pre-AKI proteinuria data.[24–27] Similarly, a recent study in adults with dialysis-requiring AKI showed a 42% prevalence of albuminuria during the follow-up period, but lacked information on prehospitalization proteinuria.[28] Because proteinuria is a known risk factor for AKI,[29,30] it is unclear whether baseline proteinuria is an unaccounted for confounder predisposing these patients to AKI, or whether AKI itself increases the risk for developing incident or progressive proteinuria.

Because proteinuria is a prognostic indicator and a modifiable risk factor in CKD progression, determining whether AKI is associated with incident or progressive proteinuria is an important step toward understanding the link between AKI and future CKD, and formulating therapeutic strategies for AKI survivors. We hypothesized that AKI is associated with both incident and progressive proteinuria. To test our hypothesis, we conducted this study within a large national, observational, matched cohort of US Veterans hospitalized between 2004 and 2012.

RESULTS

Patient characteristics

A total of 657,840 patients were eligible for the study, 115,467 of whom experienced AKI. Cohort selection is shown in Figure 1, and cohort characteristics before matching are presented in Supplementary Table S1. Optimal-distance-matching resulted in a total of 181,228 patients, with 90,614 experiencing AKI, and 90,614 not experiencing AKI. AKI and non-AKI groups were well matched (Table 1), except for severe sepsis (standardized difference, 19.4%). The proportions of patients experiencing stages I, II, or III AKI were 84% (n = 75,862), 10% (n = 9575), and 6% (n = 5177), respectively. The median patient age was 66 years [interquartile range (IQR), 59–77 yr], 98% were male, 75% were Caucasian, 48% had diabetes mellitus, and 78% had hypertension. The median baseline estimated glomerular filtration rate (eGFR) was 62 ml/min per 1.73 m^2 (IQR, 48–77 ml/min per 1.73 m^2). Fifty-six percent of the cohort had angiotensin converting enzyme inhibitor or angiotensin II receptor blocker (ACEI/ARB) prescriptions within 90 days before admission. Pre-admission proteinuria levels in the AKI and non-AKI groups were well matched, with 61% of patients in each group having no proteinuria at baseline, 17% with trace proteinuria, 12% with 1+ proteinuria, 7% with 2+ proteinuria, and 3% with 3+ proteinuria. During the 12-month follow-up period, 46% of patients had 1 urine dipstick measurement, 27% had 2 measurements, and 27% underwent 3 or more assessments.

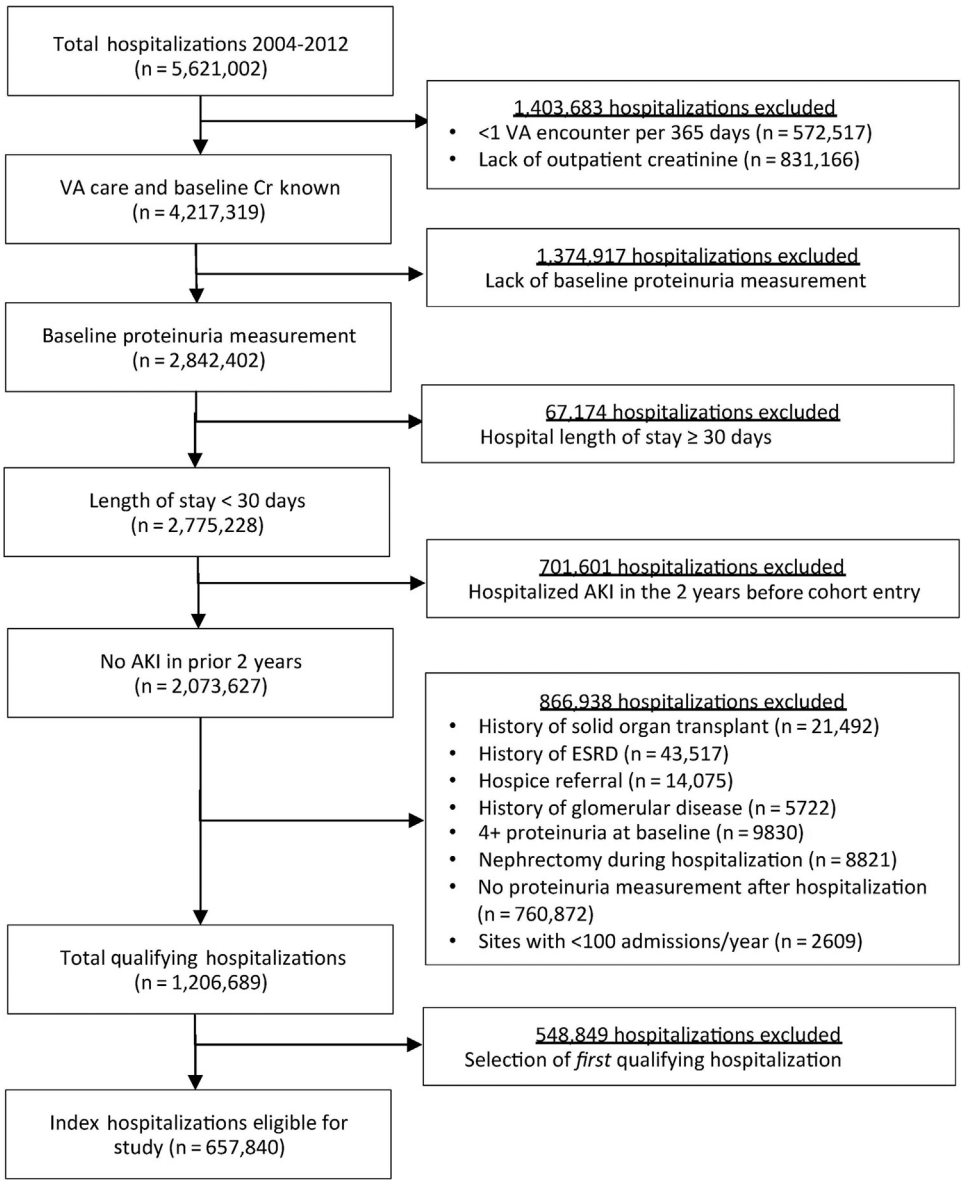

Figure 1 | Flow diagram showing selection of eligible hospitalizations for the study cohort. AKI, acute kidney injury; Cr, creatinine; ESRD, end-stage renal disease; VA, Veterans Affairs.