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# Increased risk of death and *de novo* chronic kidney disease following reversible acute kidney injury

Ion D. Bucaloiu[1], H. Lester Kirchner[2], Evan R. Norfolk[1], James E. Hartle II[1] and Robert M. Perkins[1,3]

*[1]Department of Nephrology, Geisinger Medical Center, Danville, Pennsylvania, USA; [2]Biostatistics and Research Data Core, Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA and [3]Center for Health Research, Geisinger Medical Center, Danville, Pennsylvania, USA*

**Acute kidney injury increases mortality risk among those with established chronic kidney disease. In this study we used a propensity score-matched cohort method to retrospectively evaluate the risks of death and *de novo* chronic kidney disease after reversible, hospital-associated acute kidney injury among patients with normal pre-hospitalization kidney function. Of 30,207 discharged patients alive at 90 days, 1610 with reversible acute kidney injury that resolved within the 90 days were successfully matched across multiple parameters with 3652 control patients who had not experienced acute kidney injury. Median follow-up was 3.3 and 3.4 years (injured and control groups, respectively). In Cox proportional hazard models, the risk of death associated with reversible acute kidney injury was significant (hazard ratio 1.50); however, adjustment for the development of chronic kidney injury during follow-up attenuated this risk (hazard ratio 1.18). Reversible acute kidney injury was associated with a significant risk of *de novo* chronic kidney disease (hazard ratio 1.91). Thus, a resolved episode of hospital-associated acute kidney injury has important implications for the longitudinal surveillance of patients without preexisting, clinically evident kidney disease.**

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KEYWORDS: acute kidney injury; chronic kidney disease; death; hospitalization; propensity score

**Correspondence:** *Robert M. Perkins, Center for Health Research, Geisinger Medical Center, MC 44-00, 100 North Academy Avenue, Danville, Pennsylvania 17822, USA. E-mail: rmperkins@geisinger.edu*

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Hospital-associated acute kidney injury (AKI) is common, affecting up to 1% of the general population and 15% of all hospitalized patients.[1–4] In the United States alone, more than 3 million hospitalized individuals annually are at risk.[5]

AKI is not benign; the risk of in-hospital death after such an event is increased 2.5-fold compared with similar patients without AKI,[6] and the long-term risk of death is similarly increased for subpopulations of patients with preexisting chronic kidney disease (CKD).[7] A causative relationship between AKI and these long-term risks has not been established, although it has been postulated that AKI may result in a number of systemic vascular endothelial alterations that impact cardiovascular health.[8] Whether reversible episodes of AKI represent a risk for long-term mortality in patients without underlying CKD is unknown, although these patients are not traditionally considered an at-risk population.[9]

We hypothesized that reversible changes in kidney function among hospitalized patients without preexisting, clinically evident kidney disease would increase the long-term risk of death and CKD. We assembled a cohort of hospitalized adults without evidence of kidney disease before admission, and who survived at least 90 days after discharge. Patients were stratified by AKI status, matched across a broad range of variables previously associated with AKI, and followed for the outcomes of interest.

## RESULTS

Of 39,477 individuals admitted to Geisinger Medical Center between 1 January 2004 and 31 December 2007, 30,207 patients were alive 90 days after discharge. Of these, 10,179 met at least one exclusion criterion or failed to recover kidney function after AKI. Of the remaining 20,028 individuals, 1997 met criteria for recovered AKI; 18,031 patients not experiencing AKI served as potential controls. Of the 1997 with recovered AKI, 1610 (80.6%) were successfully matched with up to 3 ($n = 3652$) controls using a $5 \rightarrow 1$ digit 'greedy' match algorithm. This served as the final study cohort.

The baseline characteristics of the two groups prior to propensity score matching are shown in Table 1. In brief, compared with controls, patients who developed AKI were older, had more comorbid conditions, lower serum albumin

**Table 1 | Baseline characteristics of hospitalized patients (2004–2007) surviving at least 90 days after discharge, by AKI status, and before matching for the propensity to develop AKI**

| | AKI group (*n*=1997) | Control group (*n*=18,031) | *P*-value[a] |
|---|---|---|---|
| *Demographic characteristic* | | | |
| Age, years; median (IQR) | 64.0 (53.0, 74.0) | 59.0 (46.0, 71.0) | <0.0001 |
| Male, *n* (%) | 951 (47.6) | 8033 (44.6) | 0.009 |
| White, *n* (%) | 1959 (98.1) | 17,688 (98.1) | 0.89 |
| Smoking history, *n* (%) | 3128 (15.9) | 3000 (16.6) | 0.42 |
| *Characteristics of index hospitalization* | | | |
| Length of hospitalization, days; median (IQR) | 6.0 (3.0, 12.0) | 2.0 (0.0, 3.0) | <0.0001 |
| Received critical care, *n* (%) | 359 (18.0) | 416 (2.3) | <0.0001 |
| Inpatient serum albumin (value closest to hospital discharge), mg/dl; median (IQR)[a] | 3.3 (2.9, 3.8) | 3.9 (3.5, 4.2) | <0.0001 |
| *Clinical characteristic* | | | |
| Baseline eGFR, ml/min per 1.73 $m^2$; median (IQR) | 97.8 (86.8, 110.8) | 96.3 (85.0, 108.5) | <0.0001 |
| Outpatient serum albumin (value closest to index admission date), mg/dl; median (IQR)[b] | 3.9 (3.5, 4.2) | 4.2 (3.9, 4.4) | <0.0001 |
| Diabetes, *n* (%) | 598 (29.9) | 3592 (19.9) | <0.0001 |
| Hypertension, *n* (%) | 1174 (58.8) | 7988 (44.3) | <0.0001 |
| Congestive heart failure, *n* (%) | 203 (10.2) | 678 (3.8) | <0.0001 |
| Atherosclerotic coronary artery disease, *n* (%) | 485 (24.3) | 2742 (15.2) | <0.0001 |
| Cardiac dysrhythmias, *n* (%) | 291 (14.6) | 1273 (7.1) | <0.0001 |
| Peripheral vascular disease, *n* (%) | 117 (5.9) | 510 (2.8) | <0.0001 |
| Stroke, *n* (%) | 192 (9.6) | 998 (5.5) | <0.0001 |
| Cancer, *n* (%) | 377 (18.9) | 1770 (9.8) | <0.0001 |
| Dementia, *n* (%) | 29 (1.4) | 157 (0.9) | 0.01 |
| Liver disease[c], *n* (%) | 38 (1.9) | 194 (1.1) | 0.001 |
| Chronic lung disease[d], *n* (%) | 366 (18.3) | 2344 (13.0) | <0.0001 |
| Obesity, *n* (%) | 185 (9.3) | 1325 (7.4) | 0.002 |
| Major infection[e], *n* (%) | 153 (7.7) | 602 (3.3) | <0.0001 |
| Renal/cardiovascular medication[f], *n* (%) | 1033 (51.7) | 8267 (45.8) | <0.0001 |
| Charlson Co-morbidity Index Score, *n* (%) | | | <0.0001 |
| 0 | 723 (36.2) | 10,110 (56.1) | |
| 1 | 532 (26.6) | 4508 (25.0) | |
| 2+ | 742 (37.2) | 3413 (18.9) | |
| *Procedure* | | | |
| Single 12-lead or 24-h electrocardiography, *n* (%) | 1673 (83.8) | 10,979 (60.9) | <0.0001 |
| Echocardiography, *n* (%) | 644 (32.2) | 3242 (18.0) | <0.0001 |
| Cardiac stress testing, *n* (%) | 164 (8.2) | 1476 (8.2) | 0.97 |
| Angiography (coronary, peripheral arterial), *n* (%) | 241 (12.1) | 1646 (9.1) | <0.0001 |
| Surgical revascularization (coronary, carotid, aortic, and peripheral arterial), *n* (%) | 130 (6.5) | 432 (2.4) | <0.0001 |
| Cardiac valvular surgery, *n* (%) | 71 (3.6) | 98 (0.5) | <0.0001 |

Abbreviations: AKI, hospital-associated acute kidney injury; CPT, Current Procedural Terminology; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Data available for 1308 (65.5%) patients in AKI group and 3498 (19.4%) controls.
[b]Data available for 1592 (79.7%) patients in AKI group and 10,686 (59.3%) controls.
[c]Chronic hepatitis, alcoholic fatty liver, hepatorenal syndrome, portosystemic encephalopathy, spontaneous bacterial peritonitis, esophageal varices.
[d]Asthma, emphysema, and chronic bronchitis.
[e]Sepsis and septicemia, intra-abdominal infections, central nervous system infections, acute and subacute endocarditis, community acquired, nosocomial, bacterial, fungal, and viral pneumonias, pyelonephritis and perinephric abscess, skin and soft tissue infections.
[f]Prescription order for any one of the following during the 6 months before index admission date: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, loop or thiazide diuretic, aldosterone antagonist, oral anticoagulant, antiplatelet agent, hydroxy-methyl–glutaryl coenzyme A reductase inhibitor, nonsteroidal anti-inflammatory agent, erythropoietin-stimulating agent, or one of the following antibiotic classes: penicillins, cephalosporins, aminoglycosides.
See Supplementary Appendix online for a comprehensive list of ICD-9-CM and CPT codes, and operational definitions, for the covariates listed.

levels, longer index hospitalizations, and a higher utilization of critical care services during the hospital stay. In all, 1137 (70.6%), 363 (22.6%), and 106 (6.6%) subjects met the Acute Kidney Injury Network stages 1, 2, and 3 criteria, respectively; only 4 subjects required temporary renal replacement therapy. Of these four, none died but two subsequently developed CKD after recovery. The duration of AKI was 24 h or less in 75% of patients, and between 2 and 4 days in 16.3%; only in 8.6% of patients did AKI fail to resolve within 4 days. Mean (s.d.) recovery estimated glomerular filtration rate (eGFR) for patients in the AKI group was 98.5 (22.0) ml/min per 1.73 $m^2$.

The matching process resulted in a final cohort that excluded those AKI cases with a greater underlying disease burden and more severe acute illness relative to those AKI cases matched with controls, as can be seen in Table 2.

Characteristics of the propensity score–matched groups are shown in Table 3. After matching, the groups were

**Table 2 | Baseline characteristics of hospitalized patients (2004–2007) with reversible AKI surviving at least 90 days after discharge, by match status**

| | Matched AKI (*n*=1610) | Unmatched AKI (*n*=387) | *P*-value[a] |
|---|---|---|---|
| *Demographic characteristic* | | | |
| Age, years; median (IQR) | 63.0 (52.0, 74.0) | 67.0 (56.0, 75.0) | 0.0003 |
| Male, *n* (%) | 753 (46.8) | 198 (51.2) | 0.12 |
| White, *n* (%) | 1582 (98.3) | 377 (97.4) | 0.27 |
| Smoking history, *n* (%) | 249 (15.5) | 69 (17.8) | 0.25 |
| *Characteristics of index hospitalization* | | | |
| Length of hospitalization, days; median (IQR) | 5.0 (3.0, 8.0) | 16.0 (10.0, 26.0) | <0.0001 |
| Received critical care, *n* (%) | 156 (9.7) | 203 (52.4) | <0.0001 |
| Inpatient serum albumin (value closest to hospital discharge), mg/dl; median (IQR)[a] | 3.5 (3.0, 3.9) | 3.0 (2.6, 3.4) | <0.0001 |
| *Clinical characteristic* | | | |
| Baseline eGFR, ml/min per 1.73 $m^2$; median (IQR) | 97.2 (86.4, 110.0) | 100.1 (88.8, 115.3) | 0.001 |
| Outpatient serum albumin (value closest to index admission date), mg/dl; median (IQR)[b] | 3.9 (3.6, 4.3) | 3.7 (3.1, 4.1) | <0.0001 |
| Diabetes, *n* (%) | 466 (28.9) | 132 (34.1) | 0.046 |
| Hypertension, *n* (%) | 929 (57.7) | 245 (63.3) | 0.044 |
| Congestive heart failure, *n* (%) | 138 (8.6) | 65 (16.8) | <0.0001 |
| Atherosclerotic coronary artery disease, *n* (%) | 366 (22.7) | 119 (30.8) | 0.0009 |
| Cardiac dysrhythmias, *n* (%) | 197 (12.2) | 94 (24.3) | <0.0001 |
| Peripheral vascular disease, *n* (%) | 82 (5.1) | 35 (9.0) | 0.003 |
| Stroke, *n* (%) | 134 (8.3) | 58 (15.0) | <0.0001 |
| Cancer, *n* (%) | 284 (17.6) | 93 (24.0) | 0.0039 |
| Dementia, *n* (%) | 19 (1.2) | 10 (2.6) | 0.038 |
| Liver disease[c], *n* (%) | 31 (1.9) | 7 (1.8) | 0.88 |
| Chronic lung disease[d], *n* (%) | 274 (17.0) | 92 (23.8) | 0.002 |
| Obesity, *n* (%) | 154 (9.6) | 31 (8.0) | 0.34 |
| Major infection[e], *n* (%) | 105 (6.5) | 48 (12.4) | <0.0001 |
| Renal/cardiovascular medication[f], *n* (%) | 815 (50.6) | 218 (56.3) | 0.043 |
| Charlson Co-morbidity Index Score, *n* (%) | | | <0.0001 |
| 0 | 606 (37.6) | 117 (30.2) | |
| 1 | 444 (27.6) | 88 (22.7) | |
| 2+ | 560 (34.8) | 182 (47.0) | |
| *Procedure* | | | |
| Single 12-lead or 24-h electrocardiography, *n* (%) | 1321 (82.0) | 352 (91.0) | <0.0001 |
| Echocardiography, *n* (%) | 506 (31.4) | 138 (35.7) | 0.11 |
| Cardiac stress testing, *n* (%) | 136 (8.5) | 28 (7.2) | 0.44 |
| Angiography (coronary, peripheral arterial), *n* (%) | 201 (12.5) | 40 (10.3) | 0.24 |
| Surgical revascularization (coronary, carotid, aortic, and peripheral arterial), *n* (%) | 90 (5.6) | 40 (10.3) | 0.0007 |

Abbreviations: AKI, hospital-associated acute kidney injury; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Data available for 941 (58.4%) patients in matched group and 367 (94.8%) unmatched.
[b]Data available for 1261 (78.3%) patients in matched group and 331 (85.5%) unmatched.
[c]Chronic hepatitis, alcoholic fatty liver, hepatorenal syndrome, portosystemic encephalopathy, spontaneous bacterial peritonitis, esophageal varices.
[d]Asthma, emphysema, and chronic bronchitis.
[e]Sepsis and septicemia, intra-abdominal infections, central nervous system infections, acute and subacute endocarditis, community acquired, nosocomial, bacterial, fungal, and viral pneumonias, pyelonephritis and perinephric abscess, skin and soft tissue infections.
[f]Prescription order for any one of the following during the 6 months before index admission date: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, loop or thiazide diuretic, aldosterone antagonist, oral anticoagulant, antiplatelet agent, hydroxy-methyl-glutaryl coenzyme A reductase inhibitor, nonsteroidal anti-inflammatory agent, erythropoietin-stimulating agent, or one of the following antibiotic classes: penicillins, cephalosporins, aminoglycosides.
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balanced across all variables but length of hospitalization. The mean age was 61 years; 47% of matched individuals were men and 15% were smokers. A substantial proportion (22%) had diabetes and/or cardiovascular disease. In all, 6% had major infections in the year before index hospitalization. Almost 10% of the matched cohort required critical care services during hospitalization.

During a median (interquartile range) follow-up of 3.3 (2.4, 4.3) years in the AKI group and 3.4 (2.6, 4.3) years in the control group, there were 144 deaths among patients with AKI and 233 deaths among controls (Figure 1). The mortality rate during this period was significantly higher in the AKI group, compared with patients without AKI: 2.8 vs. 1.9 deaths/1000 person years, respectively; mortality rate ratio (95% confidence interval (CI)) was 1.48 (1.20, 1.83, $P=0.0002$).

CKD developed in 841 patients in the AKI group and 1218 patients in the control group. The median (interquartile range) time to CKD in those experiencing AKI was 31 (2, 200) days, as compared with 140 (24, 380) days for those not experiencing AKI (Figure 2). The incident rates for CKD were

**Table 3 | Characteristics of the hospitalized cohort with normal preadmission kidney function and alive 90 days after discharge, matched for the propensity to develop AKI**

| | AKI group (*n*=1610) | Control group (*n*=3652) | Absolute standardized difference |
|---|---|---|---|
| *Demographic characteristic* | | | |
| Age, years; median (IQR) | 63.0 (52.0, 74.0) | 63.0 (51.0, 73.0) | 4.8 |
| Male, *n* (%) | 753 (46.8) | 1660 (45.4) | 0.2 |
| Whites, *n* (%) | 1582 (98.3) | 3592 (98.4) | 0.01 |
| Smoking history, *n* (%) | 249 (15.5) | 568 (15.6) | 0.03 |
| *Characteristics of index hospitalization* | | | |
| Length of hospitalization, days; median (IQR) | 5.0 (3.0, 8.0) | 4.0 (3.0, 7.0) | 19.6[a] |
| Received critical care, *n* (%) | 156 (9.7) | 267 (7.3) | 0.8 |
| Inpatient serum albumin (value closest to hospital discharge), mg/dl; median (IQR) | 3.5 (3.0, 3.9) | 3.8 (3.4, 4.1) | 3.0 |
| *Clinical characteristic* | | | |
| Baseline eGFR, ml/min per 1.73 $m^2$; median (IQR) | 97.2 (86.4, 110.0) | 97.0 (86.1, 109.7) | 2.4 |
| Outpatient serum albumin value (value closest to index admission date), mg/dl; median (IQR)[b] | 3.9 (3.6, 4.3) | 4.0 (3.6, 4.3) | 5.3 |
| Diabetes, *n* (%) | 466 (28.9) | 975 (26.7) | 0.4 |
| Hypertension, *n* (%) | 929 (57.7) | 2036 (55.8) | 0.3 |
| Congestive heart failure, *n* (%) | 138 (8.6) | 249 (6.8) | 0.6 |
| Atherosclerotic coronary artery disease, *n* (%) | 366 (22.7) | 780 (21.4) | 0.3 |
| Cardiac dysrhythmias, *n* (%) | 197 (12.2) | 394 (10.8) | 0.4 |
| Peripheral vascular disease, *n* (%) | 82 (5.1) | 172 (4.7) | 0.2 |
| Stroke, *n* (%) | 134 (8.3) | 283 (7.8) | 0.2 |
| Cancer, *n* (%) | 284 (17.6) | 564 (15.4) | 0.5 |
| Dementia, *n* (%) | 19 (1.2) | 39 (1.1) | 0.1 |
| Liver disease, *n* (%)[c] | 31 (1.9) | 45 (1.2) | 0.6 |
| Chronic lung disease, *n* (%)[d] | 274 (17.0) | 571 (15.6) | 0.3 |
| Obesity, *n* (%) | 154 (9.6) | 309 (8.5) | 0.4 |
| Major infection, *n* (%)[e] | 105 (6.5) | 214 (5.9) | 0.2 |
| Renal/cardiovascular medication, *n* (%)[f] | 815 (50.6) | 1846 (50.6) | 0.0 |
| Charlson Co-morbidity Index Score, *n* (%) | | | 9.3 |
| 0 | 606 (37.6) | 1056 (43.2) | |
| 1 | 444 (27.6) | 1017 (27.8) | |
| 2+ | 560 (34.8) | 1056 (28.9) | |
| *Procedures* | | | |
| Single 12-lead or ambulatory 24-h electrocardiography, *n* (%) | 1321 (82.0) | 2953 (80.9) | 0.1 |
| Echocardiography, *n* (%) | 506 (31.4) | 1069 (29.3) | 0.4 |
| Cardiac stress testing, *n* (%) | 136 (8.5) | 319 (8.7) | 0.1 |
| Surgical revascularization (coronary, carotid, aortic, and peripheral arterial and/or cardiac valvular surgery), *n* (%)[g] | 90 (5.6) | 181 (5.0) | 0.3 |
| Angiography (coronary and/or peripheral arterial), *n* (%) | 201 (12.5) | 473 (13.0) | 0.1 |

Abbreviations: AKI, hospital-associated acute kidney injury; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Data available for 941 (58.5%) patients in AKI group and 1876 (51.4%) controls.
[b]Data available for 1261 (78.3%) patients in AKI group and 2769 (75.8%) controls.
[c]Chronic hepatitis, alcoholic fatty liver, hepatorenal syndrome, portosystemic encephalopathy, spontaneous bacterial peritonitis, esophageal varices.
[d]Asthma, emphysema, and chronic bronchitis.
[e]Sepsis and septicemia, intra-abdominal infections, central nervous system infections, acute and subacute endocarditis, community acquired, nosocomial, bacterial, fungal, and viral pneumonias, pyelonephritis and perinephric abscess, skin and soft tissue infections.
[f]Prescription order for any one of the following during the 6 months before index admission date: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, loop or thiazide diuretic, aldosterone antagonist, oral anticoagulant, antiplatelet agent, hydroxy-methyl-glutaryl coenzyme A reductase inhibitor, nonsteroidal anti-inflammatory agent, erythropoietin-stimulating agent, or one of the following antibiotic classes: penicillins, cephalosporins, aminoglycosides.
[g]For the purposes of propensity score matching, the categories of surgical revascularization and cardiac valve surgery were combined because of the infrequency of each type of procedure.
See Supplementary Appendix online for a comprehensive list of ICD-9-CM and CPT codes, and operational definitions, for the covariates listed.

28.1 and 13.1/1000 person years in the AKI and control groups, respectively; the corresponding CKD rate ratio (95% CI) was 2.14 (1.96, 2.43), $P<0.0001$.

In the Cox proportional hazard analysis for mortality, adjusted for hospital length of stay, a reversible AKI event was associated with a 50% higher risk of death (hazard ratios (HR) 1.50; 95% CI, 1.21, 1.85, $P=0.0002$). The risk of *de novo* CKD was increased nearly twofold (HR 1.91; 95% CI, 1.75–2.09, $P<0.0001$). Adjusting for the development of CKD in the time-to-death analysis resulted in a substantial attenuation of the long-term risk conferred by an episode of reversible AKI. When incident CKD was added to the Cox

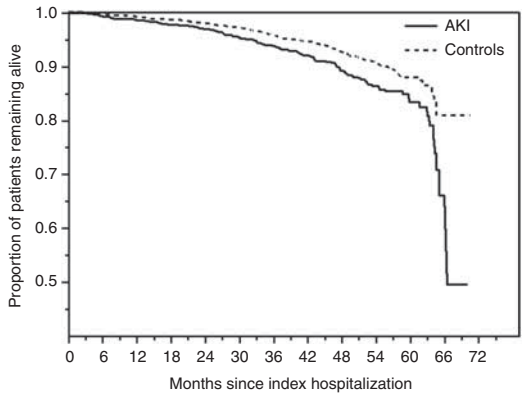


**Figure 1 | Unadjusted survival by exposure status (recovered acute kidney injury (AKI) group vs. controls) among patients with normal baseline kidney function.**

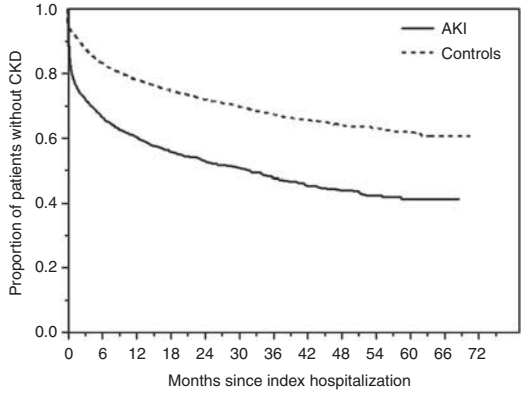


**Figure 2 | Cumulative incidence of chronic kidney disease (CKD) by exposure status (recovered acute kidney injury (AKI) group vs. controls) among patients with normal baseline kidney function.**

model for mortality as a time-dependent covariate, the HR (95% CI) for death associated with AKI was nonsignificant: 1.18 (0.95, 1.46; $P = 0.13$; Table 4). Further, within the subgroup of patients who experienced AKI, those who subsequently developed CKD had a 3.6-fold increased incidence of death compared with the group not developing CKD: mortality rate ratio (95% CI) 3.65 (2.42, 5.52, $P < 0.0001$; Table 5). A sensitivity analysis was completed using the full, unmatched cohort ($n = 20{,}028$). A multivariable Cox proportional hazard regression model was fit, which included all variables used in the propensity score model, as well as the development of CKD during follow-up. The mortality hazard associated with AKI in the multivariable regression was consistent with that observed in the primary analysis (HR = 1.15, 95% CI: 0.95, 1.39, $P = 0.16$). The results of the sensitivity analyses for definitions of AKI based on the baseline serum creatinine occurring 90 days before AKI or 30 days after AKI were similarly consistent with the primary analysis (data not shown).

The association between AKI and mortality was consistent in population subgroups (age $\geqslant 65$ years vs. younger, diabetic status, requirement for critical care services, and Charlson Co-morbidity Index score of $\geqslant 2$, vs. 0 or 1). Figure 3 shows the results of individual Cox proportional hazard survival models for each subgroup of the final, matched cohort. In each case, the model is adjusted for hospital length of stay, as well as for the development of *de novo* CKD during follow-up, in a time-dependent manner. Tests of interactions of the each subgroup and the mortality outcome were not significant (data not shown).

**Table 4 | Cox proportional hazard for time to death and *de novo* CKD (recovered AKI vs. controls)**

| | Death HR (95% CI) | *De novo* CKD HR (95% CI) |
|---|---|---|
| Adjusted for index hospital length-of-stay | 1.48 (1.19, 1.82) $P$=0.0003 | 1.91 (1.75, 2.09) $P < 0.0001$ |
| Adjusted for index hospital length-of-stay and *de novo* CKD | 1.18 (0.95, 1.46) $P$=0.13 | NA |

Abbreviations: AKI, hospital-associated acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

**Table 5 | Mortality rates among long-term hospital survivors, by AKI[a] and *de novo* CKD status**

| | No AKI, No CKD ($n$=2434) | No AKI, CKD ($n$=1218) | AKI, No CKD ($n$=769) | AKI, CKD ($n$=841) |
|---|---|---|---|---|
| No. of deaths | 102 | 131 | 28 | 116 |
| Person years follow-up | 8155.2 | 4287.4 | 2429.8 | 2756.0 |
| Mortality rate, no. of deaths/1000 person years | 12.5 | 30.6 | 11.5 | 42.1 |

Abbreviations: AKI, hospital-associated acute kidney injury; CKD, chronic kidney disease.
[a]Patients with and without AKI were matched across a broad range of covariates for the propensity to develop AKI. All patients had no evidence of CKD at baseline; 'CKD' in this table refers to the development of CKD during follow-up after recovery from AKI.

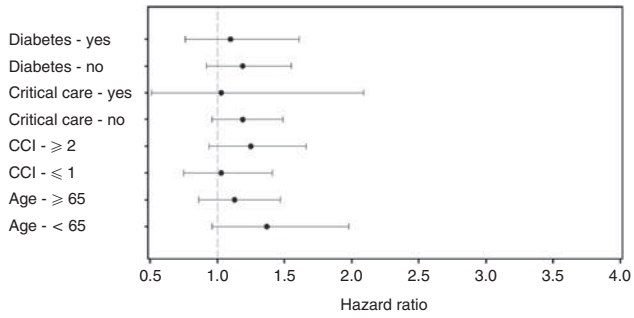


**Figure 3 | Cox proportional hazard survival (recovered acute kidney injury vs. controls) by cohort subgroups.** These models were developed for each specified subgroup from the final matched cohort ($n = 1610$ and 3652 cases and controls, respectively). Each model is adjusted for index hospital length of stay, as well as for the development of chronic kidney disease during follow-up, as in the primary analysis. CCI, Charlson Co-morbidity Index.

**Table 6 | Predictors of *de novo* CKD by Cox proportional hazard analysis among propensity score–matched patients experiencing AKI (*n*=1610)**

| Covariate | HR (95% CI) | *P*-value |
|---|---|---|
| Age, per year | 1.01 (1.01, 1.02) | 0.0004 |
| Baseline eGFR, per ml/min increase | 0.97 (0.96, 0.97) | <0.0001 |
| *Charlson Co-morbidity Index Score* | | |
| 1 vs. 0 | 1.38 (1.15, 1.66) | 0.0006 |
| 2+ vs. 0 | 1.46 (1.22, 1.75) | <0.0001 |
| Echocardiogram during 12 months before index admission date | 1.14 (0.98, 1.32) | 0.09 |
| Serum albumin test ordered during 12 months before index admission date | 4.27 (2.38, 7.67) | <0.0001 |
| Baseline outpatient serum albumin, per 1.0 g/dl increase | 0.74 (0.64, 0.85) | <0.0001 |
| CHF | 1.28 (1.03, 1.60) | 0.03 |
| Hypertension | 1.28 (1.10, 1.51) | 0.002 |
| *AKI stage*[a] | | |
| 2 vs. 1 | 1.78 (1.52, 2.09) | <0.0001 |
| 3 vs. 1 | 1.58 (1.23, 2.05) | 0.0003 |
| Hospital LOS, per day | 1.00 (1.00, 1.01) | 0.02 |

Abbreviations: AKI, hospital-acquired acute kidney injury; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; LOS, length of stay.
[a]HA-AKI stage (1, 2, or 3) was defined by the peak increase in serum creatinine during the hospitalization relative to baseline (⩾150 to <200%, ⩾200 to <300% or ⩾300% or requiring renal replacement therapy, respectively).

Predictors of *de novo* CKD among the matched AKI subcohort are shown in Table 6. Older age and a history of hypertension, congestive heart failure, and higher Charlson score at the time of index admission all predicted subsequent CKD, as did a longer index hospitalization and incremental severity of AKI. Higher baseline serum albumin and eGFR each were associated with a lower risk of *de novo* CKD during longitudinal follow-up.

## DISCUSSION

This study evaluated the long-term risks of death and *de novo* CKD following reversible AKI among adults without clinically evident renal disease both before and after the insult. We found that despite fairly rapid recovery of renal function, such episodes—involving largely modest increases in serum creatinine—were associated with a 90% increased risk of developing CKD during longitudinal follow-up. In addition, whereas patients suffering from AKI were at higher risk of death after recovery, the risk associated with the AKI event was significantly attenuated after adjustment for the development of subsequent CKD.

These results suggest that this population of patients without apparent underlying renal disease—a group traditionally considered low risk—is nonetheless at risk for clinically important long-term outcomes.[10] In particular, those who subsequently developed CKD in this cohort after resolved AKI incurred substantial mortality risk. The differential impact of AKI and CKD on mortality risk in our cohort is highlighted by a comparison of mortality rates by categories of AKI and CKD, as shown in Table 5. Despite near-equivalent death rates for those matched patients with and without AKI who do not subsequently develop CKD, the more-than-threefold increased risk of death for those matched patients with AKI who developed CKD relative to the non-AKI controls who did not develop CKD is striking. The observation that the mortality risk associated with AKI in this population is largely attenuated by the development of CKD is consistent with a large body of literature linking CKD itself with an increased risk of death, relative to those with normal kidney function.[11–13]

An association between AKI and long-term mortality has previously been observed among patients with established CKD, or in mixed populations with and without CKD. This relationship appears to be consistent both among those with more severe, dialysis-requiring AKI[14,15] and those with less severe cases of AKI.[16–20] A recent meta-analysis of 48 studies evaluating long-term outcomes after AKI determined that AKI of any severity was associated with a doubling of long-term mortality risk compared with individuals who have not experienced AKI.[7] In addition, an observational cohort of US veterans with a low (4%) prevalence of CKD (defined by ICD-9 criteria) before AKI found that after a median follow-up of 2.3 years, an AKI event was associated with a twofold increased risk of death. Adjustment for post-discharge eGFR only modestly attenuated the risk estimate.[18] Bihorac *et al.*[21] identified a long-term, 20% increased (adjusted) risk of death after AKI among postoperative patients without kidney disease before surgery; this risk was similar for the subpopulation with renal recovery, although recovery was defined liberally as a post-AKI serum creatinine level up to 50% higher than baseline. We suspect that the difference in definition of recovery explains the discrepancy in mortality risk between this study and the results we report. Our study findings are not inconsistent with those of Wald *et al.*,[22] who found no association between AKI and the long-term risk of death among those who required renal replacement therapy for AKI but recovered sufficient function to discontinue therapy within 30 days. As the cohort definition, AKI severity, and classification of recovery were quite different in this analysis compared with ours, caution is advised in drawing comparisons between the two analyses. The findings we report would suggest that any long-term mortality risk among patients with recovered AKI is largely influenced by the subsequent development of CKD rather than the AKI event itself.

CKD, when it developed, occurred relatively early after hospital discharge in this cohort. Whether this represents the natural history of AKI as it pertains to the development of subsequent CKD, or to limitations of estimating recovery from AKI based on serum creatinine-based criteria[23] (e.g., an overestimation of true GFR by serum creatinine-based criteria influenced by volume status or other factors), is not clear. Others have reported on the subsequent development of advanced CKD after AKI. Lo *et al.*[24] reported on the development of stage 4 or 5 CKD among those with baseline GFR above 45 ml/min who suffered dialysis-requiring AKI

but recovered sufficient function to discontinue treatment within 30 days. Relative to controls, those exposed were 28 times more likely to develop advanced CKD in adjusted models. As in our analysis, the outcome developed soon after discharge in a large proportion of exposed patients.

We also identified risk factors for the subsequent development of CKD among survivors of AKI. Among previously reported risk factors for CKD, such as hypertension, older age, and congestive heart failure, stage of AKI (using the Acute Kidney Injury Network staging criteria) and a physician's order for measurement of serum albumin within the prior 12 months predicted longitudinal CKD development. These factors are quite similar to those recently reported by Chawla *et al.*,[25] and we agree with their supposition that identifying at-risk patients at the time of hospital discharge using these commonly available characteristics may allow for the timely implementation of appropriate screening and surveillance.

Potential limitations of this study should be considered. Because of the observational nature of our study, we cannot exclude the possibility that unmeasured factors related to both the exposure and outcomes resulted in biased estimates of the impact of AKI. However, to limit the potential for both confounding and bias, we used propensity score matching across a broad set of demographic and clinical characteristics to establish the study cohort. In addition, our study population—from a single integrated health-care system in Central Pennsylvania—is not necessarily representative of hospitalized populations in the US or elsewhere, and the results should therefore be interpreted within that context. The matching process, as expected, resulted in a final cohort that includes those AKI cases with relatively mild underlying disease burden and lower severity of acute illness relative to the AKI cases that did not successfully match; care should therefore be taken when extrapolating these study findings. Finally, the analyses are based on non-protocolized sampling of lab values included in the modeling for this community-based cohort; although we accounted for the absence of these specific lab tests using validated statistical methods, the potential for indication bias may have influenced the study results.

In summary, reversible episodes of AKI in patients without preexisting kidney disease have important prognostic value. If confirmed in other populations, given the large absolute numbers of hospitalized patients experiencing AKI worldwide, the impact and utility of management strategies for primary CKD prevention among those patients without preexisting CKD who experience AKI would warrant further investigation.

## MATERIALS AND METHODS

This project was approved by the Geisinger Institutional Review Board on 9 February 2010. The study data source was Geisinger's electronic health record, EpicCare, which contains detailed demographic, procedural, laboratory, radiographic, vital, and other clinical data for more than 3.5 million patients receiving care at Geisinger Health System, an integrated health-care system in Central Pennsylvania.[26]

### Design and participants

A propensity score–matched cohort was developed. First, we identified all adults (18–88 years) who were discharged from Geisinger Medical Center between 1 January 2004 and 31 December 2007, and who were alive 90 days after discharge. The index hospitalization was the first hospitalization after 1 January 2004 during which AKI occurred for the exposed group, and the first hospitalization after 1 January 2004 for patients without evidence of AKI throughout the entire study period. We excluded all patients with one or more eGFR values below 60 ml/min per 1.73 $m^2$ in the year before index admission, all patients with hematuria ('trace' blood or greater by semiquantitative dipstick analysis), proteinuria (semiquantitative dipstick analysis result of 30 mg/dl or greater, a urinary protein-to-creatinine ratio greater than 0.2 mg protein per g creatinine, or a 24-h urine collection with at least 300 mg protein), microalbuminuria (defined as a random urine albumin-to-creatinine ratio greater than 30 mg per g creatinine, or a 24-h urine albumin above 30 mg), or any of the following procedures or conditions documented in the medical record during the year preceding the index hospitalization: renal replacement therapy (any prior hemodialysis or peritoneal dialysis; Current Procedural Terminology (CPT) 90935, 90937, 90945, 90947, 90960–90962, 90966, 90970, or ICD-9-CM 585.5 or 585.6), history of autosomal dominant polycystic kidney disease (ICD-9-CM 753.12 or 753.13), unilateral nephrectomy (CPT 50300, 50320, 50323, 50325, 50327–50329 or ICD-9-CM 593.83), or any solid-organ or bone marrow transplant. Patients discharged from the hospital within 30 days before the index admission and women who had any pregnancy-related diagnosis within 90 days before or 90 days after the index hospitalization were also excluded.

We calculated patient-specific propensity scores for an episode of AKI using a non-parsimonious, binary logistic regression method.[27–29] We considered the 12 months before the index hospitalization for comorbid conditions (defined by the presence of an ICD-9-CM diagnosis for a given condition associated with at least two distinct outpatient encounters, or listed on the medical problem list), procedures and surgeries (using CPT codes), and major infections; and 6 months prior for medications (using electronic prescription records). Factors present during the hospitalization itself (length of stay, requirement for critical care services, and serum albumin level closest and before discharge date) were also included. Specifically, we assessed demographic characteristics; smoking status ('ever' vs. 'never'); the Charlson Co-morbidity Index;[30] comorbid conditions such as diabetes, hypertension, coronary artery disease, congestive heart failure, cardiac dysrhythmia, peripheral vascular disease, cancer, dementia, chronic liver disease (chronic hepatitis, alcoholic fatty liver, hepatorenal syndrome, portosystemic encephalopathy, spontaneous bacterial peritonitis, esophageal varices), COPD, asthma, and obesity; major infections (sepsis and septicemia, intra-abdominal infections, CNS infections, acute and subacute endocarditis, community acquired, nosocomial, bacterial, fungal, and viral pneumonias, pyelonephritis and perinephric abscess, and skin and soft tissue infections); laboratory tests (baseline eGFR as described below, serum albumin within 3 months before the hospital admission; cardiovascular testing (electrocardiogram, echocardiogram, cardiac stress testing) and procedures (coronary angiography); cardiovascular surgical interventions (coronary, carotid, aortic, or other peripheral arterial revascularization); and a prescription for one or more medications associated with renal or cardiovascular disease. A detailed list of ICD-9-CM and CPT codes, and medications, along with operational definitions for all variables, is available in Supplementary Appendix online.

### Exposure

The study exposure was AKI, defined as a 50% increase relative to baseline occurring during hospitalization.[18,31,32] Baseline serum creatinine was defined as the lowest value recorded between 3 months before the index admission date and 30 days after the hospital discharge date. In patients without a serum creatinine measurement within 90 days preceding the hospitalization, the lowest value between the index admission date and 30 days after discharge was used to define baseline kidney function.[32] 'Recovery' of renal function was defined as an eGFR value within at least 90% of baseline eGFR occurring within 90 days of AKI. All GFR values were estimated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation,[33] based on serum creatinine values measured using the isotope dilution/mass spectroscopy traceable Roche enzymatic method.[34] Baseline eGFR was the value derived from this formula using the baseline serum creatinine, as defined above. Two sensitivity analyses were performed whereby those cases defined using a baseline serum creatinine occurring within the 90-day pre-AKI window, and those occurring within the 30-day post-AKI window, were analyzed separately in an adjusted Cox proportional hazard model.

Subjects were followed up from the date of recovery eGFR (if experiencing AKI) or date of index hospital discharge (if not experiencing AKI) until death or the end of the study period (31 December 2009).

### Outcomes

The primary study outcome was death. Vital status is coded in the Geisinger database as a distinct data field, and is updated monthly using the Social Security Administration's data set through the National Technical Information Service.[35] The secondary outcome was the development of CKD, defined as the occurrence of two or more eGFR values $\leqslant 59$ ml/min per 1.73 $m^2$, separated in time by at least 90 but no more than 365 days. The date of first occurrence was then considered the onset of *de novo* CKD.

### Statistical methods

For the purposes of baseline comparison, all qualifying patients were stratified by the presence or absence of AKI during the index hospitalization. Continuous variables were assessed for deviations against a normal distribution using Quantile–Quantile plots. Data are presented as mean and standard deviation for normally distributed, continuous variables, median and interquartile range for non-normally distributed variables, and as frequency and percentages for categorical variables. Comparisons between groups were made using the Wilcoxon nonparametric and Pearson's $\chi^2$ tests. For each individual patient, a propensity score for the development of AKI was estimated using logistic regression, treating development of AKI as the outcome. Patient demographic and clinical characteristics thought to influence either exposure status or outcomes were selected for inclusion in the model (Supplementary Appendix online). Individuals experiencing AKI were matched with up to three controls using a $5 \rightarrow 1$ digit 'greedy' match algorithm.[36] Post-matching comparisons between groups were made using the standardized difference, a technique that is independent of the sample size.[37] A standardized difference $<10$ was considered an acceptable balance between groups.[37] Incident rates for mortality and CKD were expressed as the number of events per 1000 person years. The Poisson regression model was used to estimate and compare the incidence rates, and presented as incidence rate ratios with corresponding 95% CI. Crude survival was estimated for those with AKI and controls using the Kaplan–Meier method.

Death and CKD were then each analyzed in a time-to-event manner, using a Cox proportional hazard regression model with a robust sandwich estimate of the variance to account for the inherent correlation due to the matching process. Results are expressed as HRs and corresponding 95% CIs. Post-matching variables with a standardized difference between matched groups greater than 10 were adjusted for in the multivariate Cox proportional hazards model. In addition, because of the association of CKD with death, we added *de novo* CKD as a time-dependent covariate to the Cox model. Subgroup analyses were performed based on age, diabetic status, receipt of critical care services during the index hospitalization, and Charlson Co-morbidity Index Score. These subgroup analyses were similarly adjusted for both imbalanced baseline covariates and CKD developing during follow-up. Variability of the group effect was assessed using interactions between subgroups of interest and the group indicator within the Cox proportional hazard regression model.

For outpatient and inpatient serum albumin levels, because more than 10% of the cohort did not have a test order for these parameters, we created a dummy variable to indicate whether or not the test was ordered, and included these dummy variables in the univariate and adjusted models, as appropriate.[38]

Because of the effect of matching on cohort size and the potential bias introduced by loss of cases, an additional sensitivity analysis was performed whereby the unmatched cohort was used in a multivariable Cox proportional hazard regression model to determine the association between AKI and long-term mortality. Covariates used in this sensitivity analysis included all variables used in propensity score matching, as well as in the development of CKD during follow-up, in time-dependent manner.

Finally, because of the strong association of subsequent CKD development and mortality risk among survivors of AKI, a Cox proportional hazard regression model was developed to identify factors present at the time of index hospitalization among those experiencing AKI, which independently predicted subsequent CKD development. For this analysis, the same variables used to compare the AKI and control groups at baseline were used as potential predictors of *de novo CKD*. Those specific variables that were significant at $P \leqslant 0.10$ in the univariate analysis were entered into the Cox model and sequentially eliminated using a backward stepwise approach.

Analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC).

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

**Appendix.** Death and *de novo* chronic kidney disease after reversible acute kidney injury: a propensity score–matched cohort study. Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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