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## Authors
Liu, Kathleen D
Yang, Jingrong
Tan, Thida C
et al.

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# Risk Factors for Recurrent Acute Kidney Injury in a Large Population-Based Cohort

**Kathleen D. Liu, MD, PhD**[1], **Jingrong Yang, MA**[2], **Thida C. Tan, MPH**[2], **David V. Glidden, PhD**[3], **Sijie Zheng, MD, PhD**[4], **Leonid Pravoverov, MD**[4], **Chi-yuan Hsu, MD, MSc**[1,2,3], **Alan S. Go, MD**[1,2,3,5]

[1]Division of Nephrology, Department of Medicine, University of California, San Francisco

[2]Division of Research, Kaiser Permanente Northern California, Oakland, CA

[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

[4]Department of Nephrology, Kaiser Permanente Oakland Medical Center, Oakland, CA

[5]Departments of Medicine and Health Research and Policy, Stanford University School of Medicine, Stanford, CA

## Abstract

**Rationale and objective:** Acute kidney injury (AKI) has numerous sequelae. Repeated episodes of AKI may be an important determinant of adverse outcomes, including chronic kidney disease and death. In a population-based cohort study, we sought to determine the incidence of and predictors for recurrent AKI.

**Study Design:** Retrospective cohort study.

Correspondence to: Kathleen D. Liu, MD, PhD, Division of Nephrology, Box 0532, University of California, San Francisco, San Francisco, CA 94143-0532, Tel: 415-502-7998, Fax: 415-376-3381, Kathleen.liu@ucsf.edu.

Authors' Contributions: research idea and study design: KDL, JY, TCT, CYH, ASG; data acquisition: JY, TCT, ASG; data analysis/ interpretation: KDL, JY, TCT, DVG, SZ, LP CYH, ASG; statistical analysis: JY, ASG. 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.

Supplementary Material Descriptive Text for Online Delivery

Supplementary Figure S1 (PDF). Baseline characteristics for hospitalized adult Kaiser Permanente Northern California members who experienced recurrent AKI and matched controls.

Supplementary Item S1 (PDF). Multivariable predictors of all cause mortality in adults hospitalized between 2006-2013 who experienced an episode of AKI; those with recurrent AKI were matched to controls on time since first AKI event, age, and sex.

Supplementary Table S1 (PDF). Multivariable predictors of recurrent AKI in adults hospitalized between 2006-2013 with AKI, excluding those without an outpatient baseline serum creatinine for the recurrent AKI hospitalization.

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**Setting and Participants:** 38,659 hospitalized members of Kaiser Permanente Northern California who experienced an episode of AKI from 2006-2013.

**Predictors:** Demographic, clinical and laboratory data including baseline kidney function, proteinuria and hemoglobin level, comorbidities, as well as severity of AKI.

**Outcomes:** Incidence and predictors of recurrent AKI.

**Analytical Approach:** Multivariable Cox proportional hazard regression.

**Results:** 11,048 (28.6%) experienced a second hospitalization complicated by AKI during follow-up (11.2 episodes per 100 person-years), with the second episode of AKI occurring a median of 0.6 (interquartile range, 0.2-1.9) years after the first hospitalization. In multivariable analyses, older age, black race and Hispanic ethnicity were associated with recurrent AKI, along with lower eGFR, and proteinuria and anemia. Concomitant conditions including heart failure, acute coronary syndrome, diabetes, and chronic liver disease were also multivariable predictors of recurrent AKI. Those who had higher acuity of illness during the initial hospitalization were more likely to have recurrent AKI, but greater AKI severity of the index episode was not independently associated with an increased risk of recurrent AKI. In a multivariable analysis of matched patients, recurrent AKI was associated with an increased rate of death (HR, 1.66; 95% CI, 1.57-1.77).

**Limitations:** Analyses were based on clinically available data, rather than protocol-driven, timed measurements of kidney function.

**Conclusions:** Recurrent AKI is a common occurrence after a hospitalization complicated by AKI. Based on routinely available patient characteristics, our findings could facilitate identification of the subgroup of AKI patients who may benefit from more intensive follow-up to potentially avoid recurrent AKI episodes.

### Keywords

acute kidney injury (AKI); recurrent AKI; risk factor; risk stratification; renal function; hospitalization; community-based cohort

## Introduction

Acute kidney injury (AKI) is a common complication of hospitalized patients, with associated short and long-term sequelae, including increased risks of death and developing end-stage renal disease (ESRD).[1-3] Conceptually, patients who have had one AKI episode are likely to be at greater risk for recurrent AKI, and repeated episodes of AKI may be an important determinant of incident chronic kidney disease (CKD), progression of pre-existing CKD, and ESRD. AKI is associated with longer length of a hospital stay and a higher risk of any rehospitalization [4, 5] and it is possible that recurrent AKI may be an important contributor to higher readmission rates.

However, relatively little is known about the epidemiology of recurrent AKI in representative populations. The incidence of recurrent AKI was recently described in a cohort of 11,683 individuals who suffered an episode of AKI within the Veterans Administration healthcare system.[6] Selected demographic characteristics and comorbid

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conditions, along with pre-AKI estimated glomerular filtration rate (eGFR) and hypoalbuminemia were associated with an increased risk of recurrent AKI over the subsequent 12 months. However, that study population was limited by inclusion of primarily older male veterans with limited racial/ethnic diversity and follow-up time only up to 1 year.

To address these issues, we examined the rate and independent predictors of recurrent AKI in a diverse community-based cohort of adults within a large integrated health care delivery system in Northern California.

## Methods

### Study sample

The source population included members of Kaiser Permanente Northern California. The membership is highly representative of the local surrounding and statewide population.[7, 8] The study sample included all adult (age ≥20 years) health plan members who were hospitalized at any of 21 Kaiser Permanente Northern California hospitals between January 2006 and December 2013; had at least 12 months of continuous membership and pharmacy benefit at the time of admission; had at least one valid serum creatinine value during the index hospitalization (which was the first admission during the study period); and survived to hospital discharge (Figure 1). Hospitalizations were excluded if the patient had a history of renal replacement therapy identified from the comprehensive health plan ESRD treatment registry.

The study was approved by institutional review boards of Kaiser Permanente Northern California and the University of California, San Francisco, and waiver of consent was obtained due to the nature of the study.

### Identification of AKI

We defined an episode of AKI using serum creatinine-based criteria consistent with the currently recommended KDIGO (Kidney Disease: Improving Global Outcomes) guidelines.[9] For the index hospitalization, AKI was defined as a serum creatinine rise of 0.3 mg/dL or greater within 48 hours during the hospitalization or a ≥50% above a baseline, pre-admission serum creatinine. Baseline kidney function was defined as the most recent outpatient, non-emergency department serum creatinine concentration between 7 and 365 days before admission. All outpatient serum creatinine measurements were performed at the regional health plan laboratory using an IDMS-traceable assay. Urine output data were not systematically available, so definitions of AKI based on urine output were not considered.

### Follow-up and recurrence of acute kidney injury

Follow-up occurred through December 2014, with censoring due to disenrollment from the health plan, death, end stage renal disease, and/or administrative end of study follow-up. Disenrollment was defined as a continuous membership gap of 31 days or longer. Death was comprehensively identified from health plan administrative databases, hospitalization and billing claims databases, state death certificate files and Social Security Administration vital status files using previously described methods.[10, 11]

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The outcome of interest was a subsequent episode of AKI after discharge from an index hospitalization with AKI (i.e., recurrent AKI). Recurrent AKI was defined as being rehospitalized with a serum creatinine rise of 0.3 mg/dL or greater within 48 hours during the readmission or a ≥50% above a "baseline" serum creatinine. For the recurrent AKI episode, the "baseline" serum creatinine was defined as the more recent value of the following: (1) the most recent inpatient value from the index AKI admission, if it occurred within 365 days of the current admission or (2) the most recent outpatient serum creatinine 7-365 days before the current admission. This recent outpatient serum creatinine could not precede the index AKI admission and could not be obtained in an emergency department setting. If there was no "baseline" serum creatinine available for assessment of recurrent AKI, AKI was defined using only a rise in serum creatinine of more than 0.3 mg/dL over 48 hours during the hospitalization to avoid potential misclassification.

## Covariates

Information on patient age, gender and self-reported race/ethnicity was obtained from health plan electronic health records. We searched for relevant comorbid conditions up to five years before each patient's index AKI hospitalization based on inpatient and ambulatory diagnoses and procedures, laboratory test results and dispensing records from pharmacy databases. All comorbid conditions were ascertained for 5 years before the index hospitalization; body mass index, blood pressure and laboratory data were ascertained during the 365 days before the index admission. Baseline medication use was ascertained during the 120 days before admission.

We defined diabetes mellitus based on ≥1 primary inpatient discharge diagnosis or ≥2 outpatient diagnoses or receipt of an anti-diabetic drug.[12] Hypertension was defined as ≥2 ambulatory diagnoses or ≥1 outpatient diagnosis and a receipt of an anti-hypertensive agent.[11] Dyslipidemia was based on relevant ambulatory diagnoses or receipt of antilipemic medications. Smoking status (current, former, nonsmoker) at the time of admission was ascertained from information in health plan electronic health records. Systemic cancer was identified based on ≥1 primary discharge diagnosis or ≥2 ambulatory diagnoses of any malignancy other than non-melanoma skin cancer. Prior coronary heart disease was based on prior hospitalization for acute coronary syndrome, or receipt of percutaneous coronary intervention or coronary artery bypass surgery.[10, 11] Prior chronic heart failure was defined as ≥1 primary discharge diagnosis and/or ≥3 ambulatory, non-emergency department visits for heart failure.[13, 14] Prior ischemic stroke was defined as ≥1 primary discharge diagnosis.[15]

Pre-admission glomerular filtration rate (in ml/min/1.73 $m^2$) was estimated using baseline serum creatinine information described previously and the CKD-EPI equation.[16, 17] Documented proteinuria was based on positive results for ambulatory urine dipstick (1+ or greater, in the absence of a concomitant urinary tract infection).[10] We also identified the following conditions if they occurred during the index AKI hospitalization: acute heart failure, sepsis and receipt of coronary artery revascularization (percutaneous coronary intervention or coronary artery bypass surgery) using relevant diagnosis and procedure codes.[10, 13, 14, 18] As one measure of severity of acute illness, we identified patients who

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received care in the intensive care unit (ICU) and calculated the length of the stay in the ICU (in hours) as well as the overall hospitalization (in days) from administrative data sources. Finally, to further account for acute severity of illness, we calculated a validated predicted short-term mortality score, which is based on automated inpatient, outpatient and laboratory data.[19, 20]

### Statistical methods

All analyses were performed using SAS software version 9.3 (Cary, N.C.). Given the large sample size, we compared characteristics among those with and without recurrent AKI using standardized differences, which were calculated as the difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of the variable; a D value >0.1 was considered significant.[21, 22] Rate of recurrent AKI per 100 person-years during follow-up with associated 95% confidence interval was calculated overall and stratified by baseline eGFR. We examined the association between candidate variables and recurrent AKI using Cox proportional hazard models with adjustment for selected pre-admission and in-hospital covariates. Because AKI severity defined by AKI stage was not an independent risk factor for recurrent AKI, we did not examine risk factors for recurrent AKI stratified by AKI stage. We included all variables listed in Table 3 in the final models.

In sensitivity analyses, we excluded individuals where AKI was defined using a serum creatinine rise of 0.3 mg/dL or greater within 48 hours during the hospitalization for both the index and recurrent AKI episodes, or the recurrent episode alone. To examine the impact of the episode of recurrent AKI on clinical outcomes, we matched individuals who experienced an episode of recurrent AKI to controls who survived the index episode of AKI but did not experience recurrent AKI. Matching was performed based on time since first AKI event (defined in cases as the time from the day of discharge from the index hospitalization to the day of admission for the recurrent AKI episode); controls were individuals who were not censored on the “matched” days since index hospitalization discharge and had not experienced recurrent AKI), ±1 year of age, and gender.

## Results

Among 429,852 eligible adults who were hospitalized between 2006 and 2013, 38,659 (9%) patients experienced AKI during a hospitalization (Figure 1). Of those who experienced AKI and survived the index admission, 11,048 (28.6%) experienced a second episode of AKI during follow-up, for a rate of 11.2 episodes per 100 person-years. The second episode of AKI occurred a median of 0.6 (interquartile range, 0.2-1.9) years after the index hospitalization.

In descriptive analyses, patients who experienced recurrent AKI were older and had more comorbidities than those who did not experience recurrent AKI, including higher prevalences of chronic heart failure, atrial fibrillation/flutter, diabetes, and hypertension (Tables 1 **and** 2). However, there was no significant difference in the severity of the first episode of AKI (as defined by KDIGO stage) between those who did or did not experience recurrent AKI. Those who experienced recurrent AKI were also more likely to be receiving ACE inhibitor, ARB, and loop diuretic therapy before the index AKI hospitalization. Those

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with lower eGFR and with proteinuria before the index AKI episode were also more likely to experience recurrent AKI, with a stepwise relationship between baseline level of eGFR and the incidence of recurrent AKI (Figure 2).

In multivariable analyses, older age, black race and Hispanic were independently associated with recurrent AKI, along with lower baseline eGFR, higher levels of proteinuria and anemia (Table 3). Lower baseline BMI was associated with an increased risk of recurrent AKI, while higher baseline BMI was associated with a lower risk of recurrent AKI.

Multiple comorbidities were associated with an increased adjusted rate of recurrent AKI, including prior heart failure, acute coronary syndrome, ischemic stroke, diabetes, chronic liver disease, chronic lung disease, hypothyroidism, systemic cancer, and extracranial hemorrhage (Table 3). In contrast, prior coronary bypass surgery was associated with a lower adjusted rate of recurrent AKI.

Patients who were sicker during the index hospitalization (as identified by longer length of initial hospital stay or increased predicted short-term risk of death) were independently more likely to have recurrent AKI (Table 3). Interestingly, ICU stay during the index hospitalization was not associated with an increased adjusted rate of recurrent AKI after accounting for other patient characteristics.

To examine the association of recurrent AKI with adverse outcomes, we matched patients who experienced an episode of recurrent AKI to controls who did not (Table S1). Patients were matched on time since first AKI event, age, and gender. In multivariable analysis, recurrent AKI was associated with an increased rate of death (adjusted HR, 1.66; 95% CI, 1.56-1.77)(Table S2).

In sensitivity analyses, we excluded individuals where AKI was defined using a serum creatinine rise of 0.3 mg/dL or greater within 48 hours during the hospitalization for both the index and recurrent AKI episodes or the recurrent episode alone. When the 12% of patients who did not have an outpatient baseline serum creatinine measurement from the 7-365 days before the index hospitalization were excluded, we identified 7,693 episodes of recurrent AKI among the 34,024 patients who had an index AKI event (22.6%). When we excluded all episodes of recurrent AKI defined based on a ≥ 0.3 mg/dL rise in serum creatinine over a rolling 48-hour window, 8,441 of the original 38,659 subjects (21.8%) experienced an episode of recurrent AKI, and importantly, multivariable risk factors for recurrent AKI were similar across these analyses (Table 3 **and** Table S1).

## Discussion

In a large, ethnically diverse cohort of survivors of an AKI episode within 21 hospitals in an integrated healthcare delivery system, we examined the incidence of and risk factors for recurrent AKI. We found that almost 30% of these patients experienced an episode of recurrent AKI during a median follow-up of 1.8 years, highlighting the underappreciated burden of recurrent AKI episodes. Furthermore, given the size and diversity of our cohort, we could examine a large number of candidate risk factors for recurrent AKI, including

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demographic features, laboratory abnormalities, severity of illness and a wide range of comorbid conditions.

We found that several patient characteristics, including older age, black race, Hispanic ethnicity, and lower BMI were associated with an increased risk of recurrent AKI. In terms of laboratory abnormalities, lower eGFR, higher levels of proteinuria and anemia before the index AKI episode were also independent risk factors for recurrent AKI. It is not surprising that lower baseline eGFR and proteinuria are risk factors for recurrent AKI, as these are complementary measures of reduced kidney function, which is a well-established risk factor for AKI.[3, 23-28] Although eGFR may not be a modifiable risk factor for recurrent AKI, it is easy to assess and may allow for better risk-stratification of patients after an episode of AKI. While proteinuria can be reduced through the use of ACE inhibitors and angiotensin II receptor blockers, these agents are also associated with an increased risk of AKI through different pathways. Therefore, an important clinical question that remains unknown is whether all patients or a subgroup of patients with AKI would benefit from introduction of renin-angiotensin-aldosterone system inhibition to reduce proteinuria, or whether other treatments to reduce proteinuria might reduce the risk of experiencing recurrent AKI. Anemia may be both a functional marker for CKD severity, as well as a marker for other chronic diseases or disorders in key pathways (e.g., systemic inflammation) that could increase the risk of recurrent AKI. Whether identification and treatment of potentially reversible causes of anemia or treatment of anemia can positively influence the risk of recurrent AKI without causing significant adverse effects is unknown.[29]

In terms of potentially modifiable risk factors, we found that severe hypertension (i.e., systolic blood pressure >180 mm Hg) was an independent risk factor for recurrent AKI. It has been previously shown that among severely hypertensive individuals, AKI is a common complication and associated with increased morbidity and mortality. Furthermore, AKI is a risk factor for elevated blood pressure, which may create a vicious cycle predisposing to recurrent AKI.[2, 30] However, randomized controlled trials are needed to determine whether more aggressive blood pressure control during or after an episode of AKI lowers the rate of recurrent AKI.

Although several validated measures of severity of illness—including predicted mortality as well as ICU and hospital length of stay—were strongly associated with recurrent AKI, severity of AKI (as measured by KDIGO stage) was not independently associated with recurrent AKI despite a significant proportion of patients in our cohort (29.3%) having Stage 2 or 3 AKI. Interestingly, ICU stay during the index hospitalization was also not independently associated with an increased risk of recurrent AKI, perhaps because our cohort focused on survivors of the index AKI admission. In addition, patients may be admitted routinely to the ICU for post-operative care after certain types of surgery (e.g., coronary artery bypass surgery) in addition to being admitted for acute medical illness. In contrast, across all hospitalized patients, a higher predicted short-term mortality score was strongly associated with an increased, graded risk of recurrent AKI during follow-up, which is likely explained by more acutely ill patients being at higher risk for recurrent AKI. Since these patients can be readily identified, more intensive post-hospitalization monitoring may be beneficial in reducing re-hospitalization and recurrent AKI.

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Several chronic conditions were associated with a higher rate of recurrent AKI, notably heart failure and chronic liver disease. In the case of heart failure, the “cardiorenal” syndrome has been used to describe the complex interplay between acute and chronic heart and kidney dysfunction, and AKI frequently occurs concurrently with heart failure exacerbations.[31, 32] Patients with atherosclerotic cardiovascular disease (e.g., myocardial infarction or ischemic stroke) likely have an increased burden of vascular disease, and may be predisposed to recurrent AKI episodes as a result. Similarly, advanced liver failure is often punctuated by episodes of AKI,[33] though the pathogenesis of these episodes typically does not involve the hepatorenal syndrome until very end-stage liver disease but rather may be due to intravascular volume depletion in the setting of hepatic encephalopathy and ascites management or due to acute tubular necrosis in the setting of infection. Patients with systemic cancer were also at increased risk of recurrent AKI; whether or not this is due to the administration of potentially nephrotoxic chemotherapy or due to poor oral intake/malnutrition and an increased risk of pre-renal AKI is unknown.[34] Hypothyroidism has been associated with reductions in GFR in animal models and with CKD in humans, and may predispose to recurrent AKI through these mechanisms, although reductions in GFR in humans are thought to at least partially resolve with treatment of hypothyroidism.[35] Interestingly, chronic lung disease and extracranial hemorrhage were associated with an increased risk of recurrent AKI, though the mechanism for recurrent AKI is not clear with these conditions and warrants further study. In contrast, receipt of coronary bypass surgery was associated with a lower adjusted rate of recurrent AKI, and this may be because patients who have successful bypass surgery are healthier and less likely to be rehospitalized post-operatively.

To the best of our knowledge, there are only two prior published studies of recurrent AKI.[6, 36] The first was a small, two-center analysis focused on the association of nephrology follow-up with subsequent outcomes and provided limited information on how recurrent AKI was ascertained. Similar to the analysis of Siew et al.,[6] we found that age, male gender, baseline eGFR level, diabetes, malignancy, liver disease and heart failure were risk factors for recurrent AKI. In our analysis, however, we identified a number of additional risk factors for recurrent AKI. Importantly, these risk factors included hypertension, proteinuria, and anemia—three known risk factors for AKI that are all potentially modifiable. Compared to the prior study,[6] our analysis is significantly larger (38,659 versus 11,683 index cases of AKI) and focused on a more generalizable, contemporary population. In our population, the median time to recurrent AKI was longer (0.6 years vs. 0.18 years), and the incidence of recurrent AKI was 11.2 per 100 person-years, making this a common outcome after AKI.

Strengths of our study include the extended follow-up time and our large cohort size with substantial representation of those with more severe (Stage 2 and 3) AKI as well as broad demographic diversity in community-based settings. Our study is more generalizable to the broader U.S. population than studies focusing only on patients enrolled in the Veteran Affairs administration, and our follow-up time extended beyond one year. As our analyses were based on clinically available serum creatinine data, ascertainment of baseline kidney function for evaluating recurrent AKI relied on measurements obtained as part of routine clinical care, which were perhaps more likely to be available on sicker patients. Although urine output data were not used to define AKI, outside of the ICU setting, such data are not

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systematically available, and even in the ICU, with the focus on reduction of catheter-associated urinary tract infections, hourly urine output data are becoming less available. Since our analyses relied on clinically available creatinine data, we did not classify patients as having AKI or acute kidney disease (AKD) since this is a distinction that is challenging to assign accurately with clinical data in a large population.

Nonetheless, we were able to identify several patient factors that were independently associated with an increased risk of recurrent AKI. In a sensitivity analysis where patients without data on outpatient kidney function were excluded, risk factors for recurrent AKI were unchanged. Of note, studies where AKI is defined based on diagnostic codes have been shown to be vulnerable to “code creep” and severity bias, so use of laboratory data to systematically classify recurrent AKI is a strength, despite the potential limitation of using clinical data.

We believe these findings may allow for better risk-stratification of survivors of AKI in order to potentially guide more personalized follow-up recommendations such as more intensive follow-up and avoidance of nephrotoxic exposures for those who are at higher predicted risk of recurrent AKI. Over the 8 years of follow-up time for our analysis, almost 5000 individuals/year survived an episode of hospitalized AKI. Given the large number of AKI survivors, it is critical that resources be focused on those at highest risk of complications, including recurrent AKI, and development of strategies that optimize clinical outcomes after an initial episode of AKI.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney international. 2012;81(5):442–448. [PubMed: 22113526]
2. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int 2008;74(1):101–107. [PubMed: 18385668]
3. Lo LJ, Go AS, Chertow GM, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76(8):893–899. [PubMed: 19641480]
4. Silver SA, Long J, Zheng Y, Chertow GM. Cost of Acute Kidney Injury in Hospitalized Patients. J Hosp Med 2017;12(2):70–76. [PubMed: 28182800]
5. Silver SA, Harel Z, McArthur E, et al. 30-Day Readmissions After an Acute Kidney Injury Hospitalization. Am J Med 2017;130(2):163–172 e164. [PubMed: 27751901]
6. Siew ED, Parr SK, Abdel-Kader K, et al. Predictors of Recurrent AKI. J Am Soc Nephrol 2016;27(4):1190–1200. [PubMed: 26264853]

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7. Krieger N Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992;82(5):703–710. [PubMed: 1566949]
8. Gordon NP. Characteristics of Adult Health Plan Members in the Northern California Region Membership, as Estimated from the 2011 Member Health Survey Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA 2013.
9. KDIGO AKI Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1–138.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296–1305. [PubMed: 15385656]
11. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010;362(23):2155–2165. [PubMed: 20558366]
12. Selby JV, Ray GT, Zhang D, Colby CJ. Excess costs of medical care for patients with diabetes in a managed care population. Diabetes Care. 1997;20(9):1396–1402. [PubMed: 9283786]
13. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. JAMA. 2006;296(17):2105–2111. [PubMed: 17077375]
14. Go AS, Yang J, Ackerson LM, et al. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation. 2006;113(23):2713–2723. [PubMed: 16754803]
15. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA. 2003;290(20): 2685–2692. [PubMed: 14645310]
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604–612. [PubMed: 19414839]
17. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Annals of internal medicine. 2012;156(11):785–795, W-270, W-271, W-272, W-273, W-274, W-275, W-276, W-277, W-278. [PubMed: 22312131]
18. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the Incidence and Mortality of Severe Sepsis in the United States. Critical care medicine. 2013.
19. Liu V, Kipnis P, Gould MK, Escobar GJ. Length of stay predictions: improvements through the use of automated laboratory and comorbidity variables. Medical care. 2010;48(8):739–744. [PubMed: 20613662]
20. Escobar GJ, Greene JD, Scheirer P, Gardner MN, Draper D, Kipnis P. Risk-adjusting hospital inpatient mortality using automated inpatient, outpatient, and laboratory databases. Medical care. 2008;46(3):232–239. [PubMed: 18388836]
21. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics--Simulation and Computation. 2009;38:1228–1234.
22. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46(3):399–424. [PubMed: 21818162]
23. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS. Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol. 2009;4(5):891–898. [PubMed: 19406959]
24. James MT, Hemmelgarn BR, Wiebe N, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376(9758):2096–2103. [PubMed: 21094997]
25. James MT, Grams ME, Woodward M, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Diabetes Mellitus, and Hypertension With Acute Kidney Injury. Am J Kidney Dis 2015;66(4):602–612. [PubMed: 25975964]

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26. Grams ME, Sang Y, Ballew SH, et al. A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury. Am J Kidney Dis 2015;66(4):591–601. [PubMed: 25943717]
27. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21(10):1757–1764. [PubMed: 20671214]
28. Huang TM, Wu VC, Young GH, et al. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. J Am Soc Nephrol. 2011;22(1):156–163. [PubMed: 21115618]
29. Elliott S, Tomita D, Endre Z. Erythropoiesis stimulating agents and renoprotection: a meta-analysis. BMC Nephrol. 2017;18(1):14. [PubMed: 28077085]
30. Hsu CY, Hsu RK, Yang J, Ordonez JD, Zheng S, Go AS. Elevated BP after AKI. J Am Soc Nephrol. 2016;27(3):914–923. [PubMed: 26134154]
31. Schefold JC, Filippatos G, Hasenfuss G, Anker SD, von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol. 2016;12(10):610–623. [PubMed: 27573728]
32. Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference Nephrol Dial Transplant. 2010;25(5):1406–1416. [PubMed: 20185818]
33. Karvellas CJ, Durand F, Nadim MK. Acute Kidney Injury in Cirrhosis. Crit Care Clin 2015;31(4): 737–750. [PubMed: 26410141]
34. Rosner MH, Perazella MA. Acute Kidney Injury in Patients with Cancer. N Engl J Med 2017;376(18):1770–1781. [PubMed: 28467867]
35. Iglesias P, Bajo MA, Selgas R, Diez JJ. Thyroid dysfunction and kidney disease: An update. Rev Endocr Metab Disord 2017;18(1):131–144. [PubMed: 27864708]
36. Xie M, Iqbal S. Predictors for nephrology outpatient care and recurrence of acute kidney injury (AKI) after an in-hospital AKI episode. Hemodial Int 2014;18 Suppl 1:S7–12. [PubMed: 25330834]
37. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009; 38(6): 1228–34.
38. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46(3): 399–424. [PubMed: 21818162]

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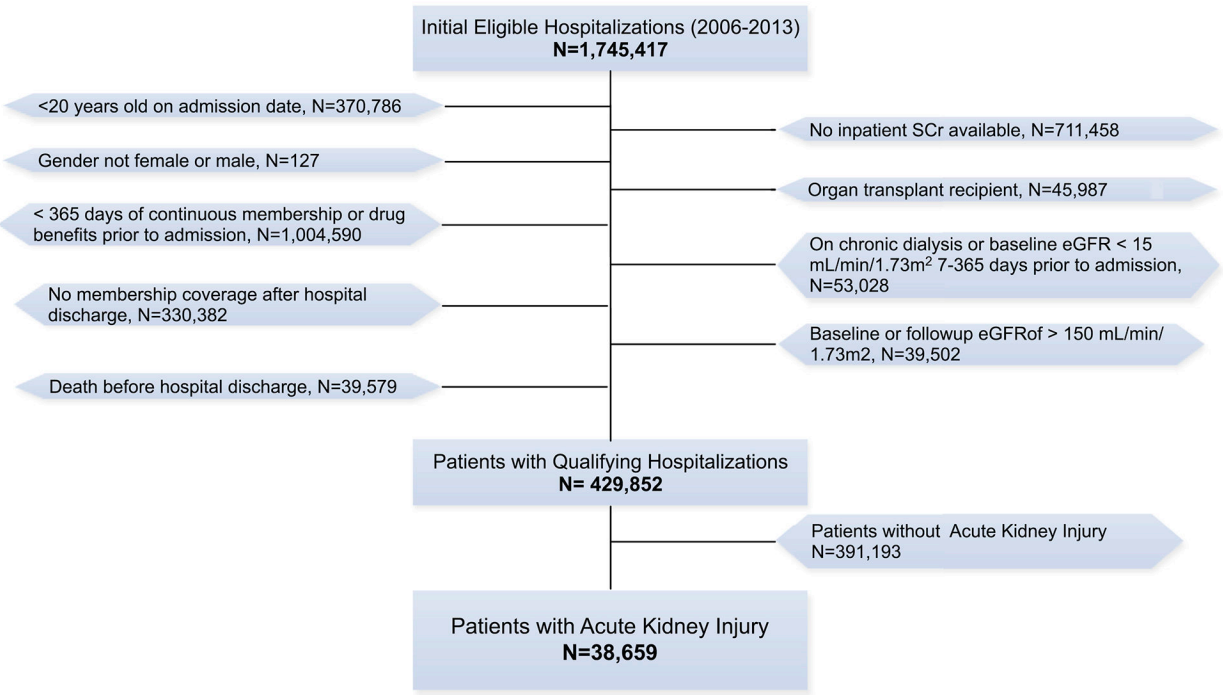


**Figure 1.**

Study sample. The study sample included all adult (age >20 years) health plan members who were hospitalized at any of 21 Kaiser Permanente Northern California hospitals between January 1, 2006 and December 31, 2013, and who had at least 12 months of continuous membership and pharmacy benefit at the time of admission; who had at least one valid serum creatinine value during the index hospitalization; and who survived to hospital discharge.

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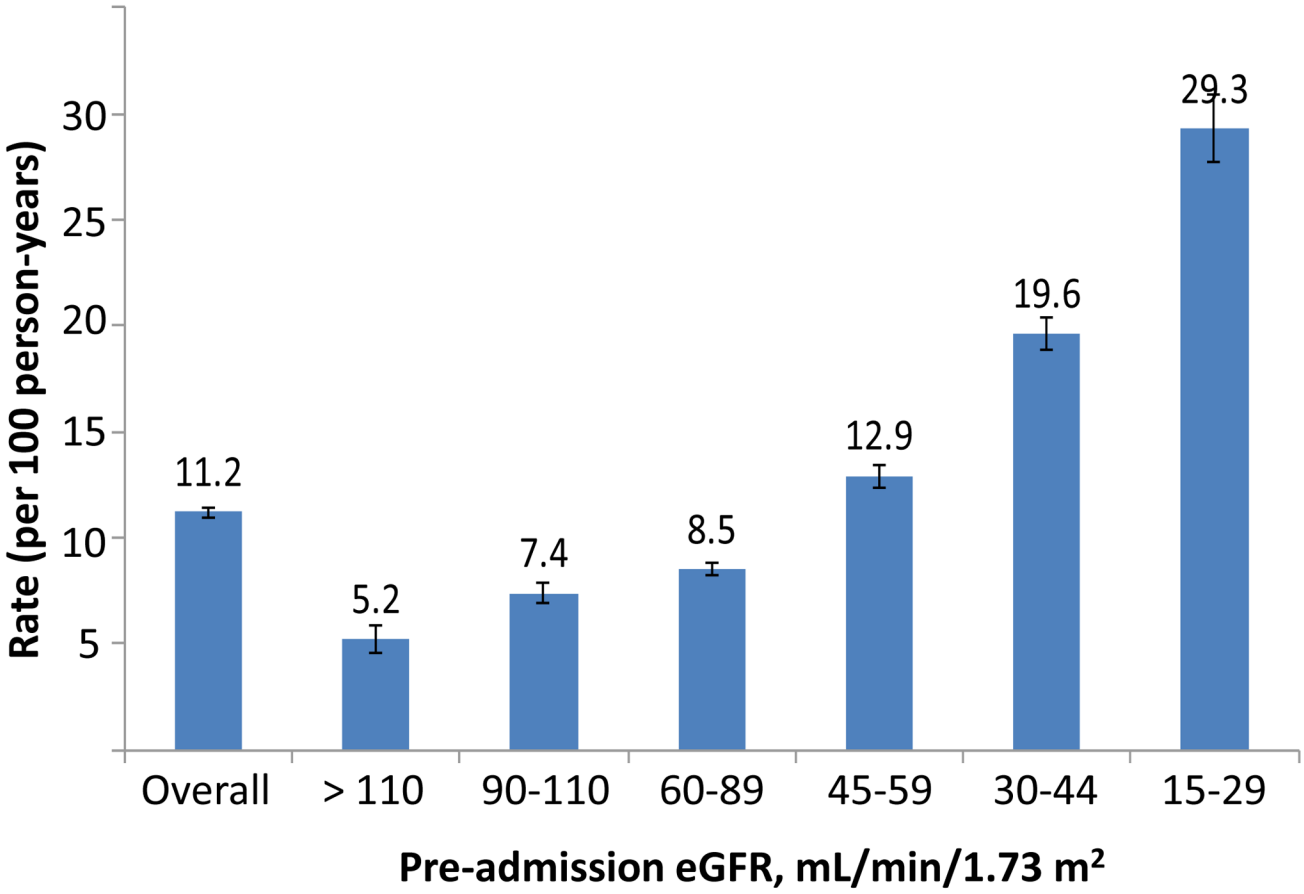


**Figure 2.**
Relationship between baseline eGFR and rate of recurrent AKI.

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**Table 1:**

Baseline characteristics for hospitalized adult Kaiser Permanent Northern California members between 2006-2013 who had AKI, stratified by recurrent AKI status after discharge

| Characteristic | Overall (N=38,659) | Recurrent AKI (N=11,048) | Non-Recurrent AKI (N=27,611) | D value |
|---|---|---|---|---|
| **Age in years** | 69.1 +/− 15.1 | 72.0 +/− 13.0 | 67.9 +/− 16.2 | **0.27** |
| **Women, n (%)** | 19,137 (49.5) | 5419 (49.0) | 13,718 (49.7) | 0.01 |
| **Race, n (%)** | | | | 0.08 |
| White | 27,669 (71.6) | 7982 (72.2) | 19,687 (71.3) | |
| Black/African American | 4404 (11.4) | 1454 (13.2) | 2950 (10.7) | |
| Asian/Pacific Islander | 4675 (12.1) | 1216 (11.0) | 3459 (12.5) | |
| Native American | 265 (0.7) | 82 (0.7) | 183 (0.7) | |
| Unknown | 1646 (4.3) | 314 (2.8) | 1332 (4.8) | |
| **Hispanic ethnicity, n (%)** | 5538 (14.3) | 1602 (14.5) | 3936 (14.3) | 0.01 |
| **Current or former smoker, n (%)** | 19,754 (51.1) | 5919 (53.6) | 13,835 (50.1) | 0.07 |
| **AKI Stage, n (%)** | | | | 0.00 |
| Stage 1 | 27,323 (70.7) | 7803 (70.6) | 19,520 (70.7) | |
| Stage 2 | 5515 (14.3) | 1560 (14.1) | 3955 (14.3) | |
| Stage 3 | 5821 (15.1) | 1685 (15.3) | 4136 (15.0) | |
| **Cardiovascular history, n (%)** | | | | |
| Acute coronary syndrome | 2794 (7.2) | 1084 (9.8) | 1710 (6.2) | **0.30** |
| Heart failure | 6694 (17.3) | 3014 (27.3) | 3680 (13.3) | **0.54** |
| Hospitalized ischemic stroke | 887 (2.3) | 323 (2.9) | 564 (2.0) | **0.22** |
| Transient ischemic attack | 917 (2.4) | 336 (3.0) | 581 (2.1) | **0.23** |
| Peripheral artery disease | 1870 (4.8) | 571 (5.2) | 1299 (4.7) | 0.06 |
| Mitral and/or aortic valvular disease | 3088 (8.0) | 1091 (9.9) | 1997 (7.2) | **0.21** |
| Atrial fibrillation and/or flutter | 5231 (13.5) | 1883 (17.0) | 3348 (12.1) | **0.24** |
| Coronary artery bypass graft surgery | 832 (2.2) | 256 (2.3) | 576 (2.1) | 0.07 |
| Percutaneous coronary intervention | 1647 (4.3) | 632 (5.7) | 1015 (3.7) | **0.28** |
| **Medical history, n (%)** | | | | |
| Diabetes mellitus | 15,315 (39.6) | 5522 (50.0) | 9793 (35.5) | **0.36** |
| Hypertension | 29,203 (75.5) | 9204 (83.3) | 19,999 (72.4) | **0.39** |
| Diagnosed dementia | 2268 (5.9) | 622 (5.6) | 1646 (6.0) | 0.04 |
| Dyslipidemia | 26,926 (69.7) | 8499 (76.9) | 18,427 (66.7) | **0.31** |
| Chronic liver disease | 1691 (4.4) | 586 (5.3) | 1105 (4.0) | **0.18** |
| Chronic lung disease | 10,396 (26.9) | 3543 (32.1) | 6853 (24.8) | **0.22** |
| Hypothyroidism | 6506 (16.8) | 2184 (19.8) | 4322 (15.7) | **0.17** |
| Systemic cancer | 9090 (23.5) | 2566 (23.2) | 6524 (23.6) | 0.01 |
| Extracranial hemorrhage | 1102 (2.9) | 426 (3.9) | 676 (2.4) | **0.28** |
| **Body mass index, , n (%)** | | | | 0.05 |

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| Characteristic | Overall (N=38,659) | Recurrent AKI (N=11,048) | Non-Recurrent AKI (N=27,611) | D value |
|---|---|---|---|---|
| < 18.5 **kg/m$^2$** | 726 (1.9) | 195 (1.8) | 531 (1.9) | |
| 18.5-24.9 **kg/m$^2$** | 8811 (22.8) | 2444 (22.1) | 6367 (23.1) | |
| 25.0-29.9 **kg/m$^2$** | 10,716 (27.7) | 2921 (26.4) | 7795 (28.2) | |
| 30.0-39.9 **kg/m$^2$** | 12,070 (31.2) | 3539 (32.0) | 8531 (30.9) | |
| ≥ 40 **kg/m$^2$** | 2609 (6.7) | 885 (8.0) | 1724 (6.2) | |
| Unknown | 3727 (9.6) | 1064 (9.6) | 2663 (9.6) | |
| **Systolic blood pressure, , n (%)** | | | | 0.01 |
| < 120 **mmHg** | 13,224 (34.2) | 3824 (34.6) | 9400 (34.0) | |
| 121-130 **mmHg** | 6734 (17.4) | 1827 (16.5) | 4907 (17.8) | |
| 131-139 **mmHg** | 8075 (20.9) | 2224 (20.1) | 5851 (21.2) | |
| 140-159 **mmHg** | 6238 (16.1) | 1874 (17.0) | 4364 (15.8) | |
| 160-179 **mmHg** | 1861 (4.8) | 612 (5.5) | 1249 (4.5) | |
| ≥ 180 **mmHg** | 701 (1.8) | 249 (2.3) | 452 (1.6) | |
| **Diastolic blood pressure, mmHg, n (%)** | | | | **0.10** |
| ≤ 80 **mmHg** | 29,558 (76.5) | 8834 (80.0) | 20,724 (75.1) | |
| 81-84 **mmHg** | 2652 (6.9) | 665 (6.0) | 1987 (7.2) | |
| 85-89 **mmHg** | 2123 (5.5) | 506 (4.6) | 1617 (5.9) | |
| 90-99 **mmHg** | 1796 (4.6) | 444 (4.0) | 1352 (4.9) | |
| 100-109 **mmHg** | 489 (1.3) | 117 (1.1) | 372 (1.3) | |
| ≥ 110 **mmHg** | 211 (0.5) | 42 (0.4) | 169 (0.6) | |
| **Baseline medication use, n (%)** | | | | |
| Angiotensin-converting enzyme inhibitor | 16,638 (43.0) | 5394 (48.8) | 11,244 (40.7) | **0.20** |
| Angiotensin II receptor blocker | 4918 (12.7) | 1649 (14.9) | 3269 (11.8) | **0.16** |
| Any diuretic | 19,558 (50.6) | 6606 (59.8) | 12,952 (46.9) | **0.32** |
| Loop | 9164 (23.7) | 3924 (35.5) | 5240 (19.0) | **0.52** |
| Thiazide | 12,249 (31.7) | 3505 (31.7) | 8744 (31.7) | 0.00 |
| Any β-blocker | 17,105 (44.2) | 5824 (52.7) | 11,281 (40.9) | **0.29** |
| Calcium channel blocker | 9339 (24.2) | 3247 (29.4) | 6092 (22.1) | **0.23** |
| Any aldosterone receptor antagonist | 1272 (3.3) | 538 (4.9) | 734 (2.7) | **0.38** |
| Alpha-blocker | 5432 (14.1) | 1926 (17.4) | 3506 (12.7) | **0.23** |
| Nitrate | 2559 (6.6) | 1152 (10.4) | 1407 (5.1) | **0.47** |
| Isosorbide dinitrate + hydralazine | 434 (1.1) | 233 (2.1) | 201 (0.7) | **0.65** |
| Hydralazine | 1786 (4.6) | 777 (7.0) | 1009 (3.7) | **0.42** |
| Antiarrhythmic | 718 (1.9) | 312 (2.8) | 406 (1.5) | **0.40** |
| Digoxin | 1763 (4.6) | 734 (6.6) | 1029 (3.7) | **0.37** |
| Statin | 19,139 (49.5) | 6308 (57.1) | 12,831 (46.5) | **0.26** |
| Other lipid-lowering agent | 2131 (5.5) | 703 (6.4) | 1428 (5.2) | **0.13** |
| Anti-inflammatory drug | 5656 (14.6) | 1534 (13.9) | 4122 (14.9) | 0.05 |

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| Characteristic | Overall (N=38,659) | Recurrent AKI (N=11,048) | Non-Recurrent AKI (N=27,611) | D value |
|---|---|---|---|---|
| Antiplatelet agent | 1965 (5.1) | 770 (7.0) | 1195 (4.3) | **0.31** |
| Diabetic therapy | 9203 (23.8) | 3435 (31.1) | 5768 (20.9) | **0.32** |
| **Baseline outpatient, non-emergency department laboratory values** | | | | |
| Serum creatinine, mg/dL | | | | |
| Mean | 1.2 +/− 0.5 | 1.3 +/− 0.5 | 1.1 +/− 0.5 | **0.33** |
| Median | 1.1 [0.8-1.4] | 1.2 [0.9-1.6] | 1.0 [0.8-1.3] | |
| eGFR, | | | | **0.19** |
| > 110 ml/min/1.73m$^2$ | 1769 (4.6) | 264 (2.4) | 1505 (5.5) | |
| 90-110 ml/min/1.73m$^2$ | 4465 (11.5) | 937 (8.5) | 3528 (12.8) | |
| 60-89 ml/min/1.73m$^2$ | 11,902 (30.8) | 2902 (26.3) | 9000 (32.6) | |
| 45-59 ml/min/1.73m$^2$ | 6911 (17.9) | 2261 (20.5) | 4650 (16.8) | |
| 30-44 ml/min/1.73m$^2$ | 5978 (15.5) | 2425 (21.9) | 3553 (12.9) | |
| 15-29 ml/min/1.73m$^2$ | 2999 (7.8) | 1265 (11.5) | 1734 (6.3) | |
| Unknown | 4635 (12.0) | 994 (9.0) | 3641 (13.2) | |
| Hemoglobin in g/dL | 12.6 +/− 2.0 | 12.3 +/− 2.0 | 12.8 +/− 1.9 | **0.21** |
| White blood cell count, 10$^3$/uL | 8.6 +/− 7.8 | 8.7 +/− 9.9 | 8.5 +/− 6.7 | 0.02 |
| **Baseline proteinuria** | | | | |
| Any urinary dipstick protein >=1+, n (%) | 20,545 (53.1) | 6632 (60.0) | 13,913 (50.4) | **0.24** |
| Most recent urinary dipstick protein result, n (%) | | | | 0.01 |
| Negative | 13,860 (35.9) | 3880 (35.1) | 9980 (36.1) | |
| Trace | 5405 (14.0) | 1405 (12.7) | 4000 (14.5) | |
| 1+ | 8024 (20.8) | 2410 (21.8) | 5614 (20.3) | |
| 2+ | 4777 (12.4) | 1542 (14.0) | 3235 (11.7) | |
| 3+ | 2349 (6.1) | 851 (7.7) | 1498 (5.4) | |
| Unknown | 4244 (11.0) | 960 (8.7) | 3284 (11.9) | |
| **Index Hospitalization** | | | | |
| ICU stay, n (%) | 12,038 (31.1) | 3549 (32.1) | 8489 (30.7) | 0.04 |
| Predicted mortality score category, n (%) | | | | **0.12** |
| < 0.001 | 1768 (4.6) | 194 (1.8) | 1574 (5.7) | |
| 0.001 < 0.005 | 4044 (10.5) | 773 (7.0) | 3271 (11.8) | |
| 0.005 < 0.02 | 9312 (24.1) | 2458 (22.2) | 6854 (24.8) | |
| 0.02 < 0.05 | 9331 (24.1) | 3128 (28.3) | 6203 (22.5) | |
| 0.05 < 0.10 | 6549 (16.9) | 2265 (20.5) | 4284 (15.5) | |
| 0.10 < 0.15 | 2733 (7.1) | 924 (8.4) | 1809 (6.6) | |
| 0.15 < 0.30 | 2576 (6.7) | 868 (7.9) | 1708 (6.2) | |
| ≥ 0.30 | 915 (2.4) | 288 (2.6) | 627 (2.3) | |

*Values for categorical variables given as count (percentage); for continuous variables, as mean +/− SD or median [interquartile range].*

Given the large sample size, standardized differences were used to compare groups; these calculated as the difference in means or proportions of a variable divided by a pooled estimate of the SD of the variable, with a value greater than 0.1 considered to be significant [37,38]

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**Table 2.**

Length of stay and acute severity of illness for hospitalized adult Kaiser Permanente Northern California members between 2006-2013 who had AKI, stratified by recurrent AKI status after discharge.

| Characteristic | Overall (N=38,659) | Recurrent AKI (n=11,048) | Non-Recurrent AKI (n=27,611) | P Value |
|---|---|---|---|---|
| Hospital length of stay in days | 6 [3-10] | 6 [4-11] | 5 [3-10] | <0.001 |
| LAPS | 27 [9-43] | 31 (17-46) | 24 (6-42) | <0.001 |
| COPS | 78 (46-114) | 93 (61-129) | 72 (42-107) | <0.001 |
| Predicted mortality score | 0.03 (0.01-0.07) | 0.04 (0.01-0.08) | 0.02 (0.01-0.07 | <0.001 |
| | | | | |

*Unless otherwise indicated, values shown are median [interquartile range].*

*AKI, acute kidney injury.*

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**Table 3.**

Multivariable predictors of recurrent AKI in adults hospitalized between 2006-2013 with AKI and sensitivity analysis excluding those without a baseline serum creatinine for the index or recurrent AKI hospitalization.

| Variable | Recurrent AKI, (11,048 of 38,659) | Recurrent AKI using only 50% rise from baseline (7,693 of 34,024) |
|---|---|---|
| **Age group** | | |
| 20-49 y | 1.00 (reference) | 1.00 (reference) |
| 50-59 y | **1.29 (1.17-1.43)** | **1.14 (1.01-1.28)** |
| 60-69 y | **1.32 (1.19-1.45)** | **1.09 (0.97-1.22)** |
| 70-79 y | **1.39 (1.26-1.54)** | **1.12 (0.99-1.26)** |
| ≥ 80 y | **1.54 (1.38-1.71)** | **1.19 (1.04-1.35)** |
| **Male sex** | **1.10 (1.06-1.15)** | **1.07 (1.02-1.13)** |
| **Race** | | |
| White | 1.00 (reference) | 1.00 (reference) |
| Black/African American | **1.15 (1.08-1.22)** | **1.10 (1.03-1.19)** |
| Asian/Pacific Islander | 0.95 (0.89-1.01) | 0.93 (0.86-1.00) |
| Native American | 1.02 (0.82-1.27) | 1.05 (0.82-1.36) |
| Unknown | **0.76 (0.67-0.86)** | **0.76 (0.66-0.88)** |
| **Hispanic ethnicity** | **1.11 (1.05-1.18)** | **1.18 (1.10-1.27)** |
| **Severity of index AKI episode** | | |
| Stage 1 | 1.00 (reference) | 1.00 (reference) |
| Stage 2 | 1.04 (0.98-1.10) | 1.05 (0.99-1.12) |
| Stage 3 | 1.02 (0.96-1.07) | 0.99 (0.93-1.06) |
| **Cardiovascular history** | | |
| Acute coronary syndrome | **1.14 (1.06-1.23)** | **1.11 (1.02-1.22)** |
| Heart failure | **1.36 (1.29-1.43)** | **1.26 (1.18-1.34)** |
| Ischemic stroke | **1.16 (1.04-1.30)** | **1.19 (1.04-1.36)** |
| Transient ischemic attack | 1.12 (1.00-1.25) | 1.14 (0.99-1.30) |
| Peripheral arterial disease | 1.06 (0.97-1.15) | 1.07 (0.96-1.18) |
| Mitral and/or aortic valvular disease | 1.01 (0.94-1.08) | 0.99 (0.91-1.07) |
| Atrial fibrillation and/or flutter | 1.03 (0.97-1.09) | 1.00 (0.94-1.08) |
| **Cardiac procedure history** | | |
| Coronary artery bypass graft surgery | **0.75 (0.66-0.85)** | **0.71 (0.61-0.83)** |
| Percutaneous coronary intervention | 1.02 (0.93-1.12) | 1.02 (0.92-1.14) |
| **Medical history** | | |
| Diabetes mellitus | **1.30 (1.23-1.37)** | **1.25 (1.17-1.33)** |
| Hypertension | **1.07 (1.01-1.14)** | **1.06 (0.98-1.14)** |
| Dyslipidemia | 1.05 (0.98-1.11) | 1.01 (0.94-1.09) |
| Chronic liver disease | **1.58 (1.44-1.72)** | **1.62 (1.47-1.79)** |
| Chronic lung disease | **1.19 (1.14-1.24)** | **1.18 (1.12-1.24)** |

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| Variable | Recurrent AKI, (11,048 of 38,659) | Recurrent AKI using only 50% rise from baseline (7,693 of 34,024) |
|---|---|---|
| Hypothyroidism | **1.09 (1.04-1.14)** | 1.05 (0.99-1.11) |
| Systemic cancer | **1.11 (1.06-1.17)** | **1.15 (1.09-1.21)** |
| Extracranial hemorrhage | **1.15 (1.04-1.26)** | **1.18 (1.06-1.33)** |
| **Body mass index,** | | |
| < 18.5 **kg/m$^2$** | **1.28 (1.11-1.48)** | **1.28 (1.07-1.52)** |
| 18.5-24.9 **kg/m$^2$** | 1.00 (reference) | 1.00 (reference) |
| 25.0-29.9 **kg/m$^2$** | **0.90 (0.85-0.95)** | **0.91 (0.85-0.97)** |
| 30.0-39.9 v | **0.93 (0.88-0.99)** | **0.96 (0.90-1.03)** |
| ≥ 40 **kg/m$^2$** | 1.00 (0.92-1.09) | 1.07 (0.97-1.18) |
| **SBP category,** | | |
| < 120 mm Hg | 1.00 (reference) | 1.00 (reference) |
| 121-130 mm Hg | 0.96 (0.90-1.01) | 0.92 (0.86-0.98) |
| 131-139 mm Hg | 0.98 (0.93-1.03) | 0.94 (0.88-1.00) |
| 140-159 mm Hg | 1.04 (0.98-1.10) | 0.99 (0.93-1.06) |
| 160-179 mm Hg | 1.07 (0.98-1.16) | 1.03 (0.92-1.14) |
| ≥ 180 mm Hg | **1.16 (1.01-1.32)** | 1.01 (0.85-1.20) |
| **Laboratory findings** | | |
| eGFR category | | |
| > 110 ml/min/1.73m$^2$ | 1.11 (0.97-1.28) | 1.00 (0.85-1.17) |
| 90-110 ml/min/1.73m$^2$ | 1.04 (0.96-1.12) | 1.02 (0.94-1.11) |
| 60-89 ml/min/1.73m$^2$ | 1.00 (reference) | 1.00 (reference) |
| 45-59 ml/min/1.73m$^2$ | **1.16 (1.10-1.23)** | **1.11 (1.04-1.18)** |
| 30-44 ml/min/1.73m$^2$ | **1.40 (1.32-1.49)** | **1.24 (1.15-1.32)** |
| 15-29 ml/min/1.73m$^2$ | **1.49 (1.38-1.60)** | **1.13 (1.03-1.24)** |
| Hemoglobin category, | | |
| > 13.0 g/dL | 1.00 (reference) | 1.00 (reference) |
| 12.0-12.9 g/dL | **1.11 (1.05-1.18)** | **1.12 (1.04-1.20)** |
| 11.0-11.9 g/dL | **1.32 (1.24-1.40)** | **1.35 (1.26-1.45)** |
| 10.0-10.9 g/dL | **1.34 (1.25-1.44)** | **1.39 (1.28-1.51)** |
| 9.0-9.9 g/dL | **1.63 (1.48-1.78)** | **1.65 (1.48-1.84)** |
| < 9.0 g/dL | **1.65 (1.48-1.83)** | **1.75 (1.55-1.98)** |
| Unknown | 1.06 (1.00-1.13) | 1.02 (0.95-1.10) |
| Urinary dipstick protein excretion | | |
| Negative | 1.00 (reference) | 1.00 (reference) |
| Trace | 1.04 (0.97-1.10) | 1.01 (0.94-1.08) |
| 1+ | **1.10 (1.04-1.16)** | **1.11 (1.05-1.18)** |
| 2+ | **1.18 (1.11-1.26)** | **1.12 (1.04-1.20)** |
| 3+ | **1.46 (1.35-1.58)** | **1.42 (1.29-1.56)** |

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| Variable | Recurrent AKI, (11,048 of 38,659) | Recurrent AKI using only 50% rise from baseline (7,693 of 34,024) |
|---|---|---|
| **Index Hospitalization** | | |
| ICU stay | **0.90 (0.86-0.95)** | **0.94 (0.88-0.99)** |
| ICU length of stay, per 1-d greater | **1.01 (1.01-1.01)** | **1.01 (1.01-1.01)** |
| Hospital length of stay | | |
| ≤ 3 d | 1.00 (reference) | 1.00 (reference) |
| 4-7 d | **1.21 (1.15-1.27)** | **1.19 (1.12-1.26)** |
| >7 d | **1.54 (1.46-1.62)** | **1.54 (1.44-1.64)** |
| Predicted mortality score category | | |
| < 0.001 | 1.00 (reference) | 1.00 (reference) |
| 0.001 < 0.005 | **1.48 (1.26-1.73)** | **1.52 (1.26-1.85)** |
| 0.005 < 0.02 | **1.85 (1.59-2.15)** | **2.00 (1.67-2.40)** |
| 0.02 < 0.05 | **2.19 (1.89-2.55)** | **2.37 (1.98-2.84)** |
| 0.05 < 0.10 | **2.30 (1.97-2.68)** | **2.55 (2.12-3.07)** |
| 0.10 < 0.15 | **2.34 (1.99-2.76)** | **2.60 (2.14-3.16)** |
| 0.15 < 0.30 | **2.60 (2.21-3.06)** | **2.92 (2.40-3.55)** |
| ≥ 0.30 | **2.60 (2.15-3.14)** | **3.05 (2.43-3.82)** |

Note: values shown are adjusted hazard ratio (95% confidence interval).

AKI, acute kidney injury; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate (as determined using the CKD-EPI creatinine equation).