Title

A prospective cohort study of acute kidney injury and kidney outcomes, cardiovascular events, and death.

Journal

Kidney international, 99(2)

ISSN

0085-2538

Authors

Ikizler, T Alp
Parikh, Chirag R
Himmelfarb, Jonathan
et al.

Publication Date

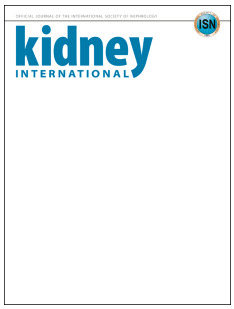
2021-02-01

DOI

10.1016/j.kint.2020.06.032

Peer reviewed

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



A prospective cohort study that examined acute kidney injury and kidney outcomes, cardiovascular events and death informs on long-term clinical outcomes.

T. Alp Ikizler, MD, Chirag R. Parikh, MD, PhD, Jonathan Himmelfarb, MD, Vernon M. Chinchilli, PhD, Kathleen D. Liu, MD, PhD, Steven G. Coca, DO, MS, Amit X. Garg, MD, PhD, Chi-yuan Hsu, MD, MSc, Edward D. Siew, MD, MSCI, Mark M. Wurfel, MD, PhD, Lorraine B. Ware, MD, Georgia Brown Faulkner, MS, RN, Thida C. Tan, MPH, James S. Kaufman, MD, Paul L. Kimmel, MD, Alan S. Go, MD, for the ASSESS-AKI Study Investigators

PII: S0085-2538(20)30826-7

DOI: https://doi.org/10.1016/j.kint.2020.06.032

Reference: KINT 2206

To appear in: *Kidney International*

Received Date: 15 November 2019

Revised Date: 20 May 2020

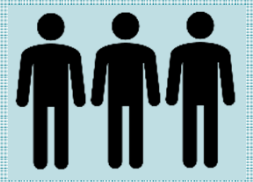
Accepted Date: 4 June 2020

Please cite this article as: Ikizler TA, Parikh CR, Himmelfarb J, Chinchilli VM, Liu KD, Coca SG, Garg AX, Hsu Cy, Siew ED, Wurfel MM, Ware LB, Faulkner GB, Tan TC, Kaufman JS, Kimmel PL, Go AS, for the ASSESS-AKI Study Investigators, A prospective cohort study that examined acute kidney injury and kidney outcomes, cardiovascular events and death informs on long-term clinical outcomes., *Kidney International* (2020), doi: https://doi.org/10.1016/j.kint.2020.06.032.

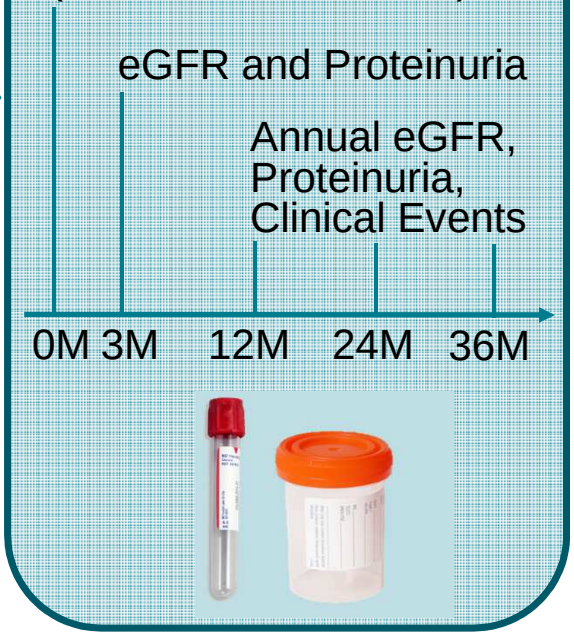
A prospective cohort study that examined acute kidney injury and kidney outcomes, cardiovascular events and death informs on long-term clinical outcomes.

Cohort

Multicenter cohort of matched adults surviving hospitalization (769 with and 769 without AKI)



Follow-Up Measurements



Associations between AKI and Clinical Outcomes

Outcome	Overall	Adjusted for 3-Mo Kidney Measures	
		No Prior CKD	Prior CKD
Incident CKD	↑	↑	-
Progressive CKD	↑	-	↑
Heart Failure	↑	↑	NS
All-Cause Death	↑	NS	↑
Major ASCVD Events	NS	NS	NS

CONCLUSION:

AKI increases risks of kidney complications, heart failure and death. Assessing kidney function and proteinuria 3 months after AKI provides important prognostic information for long-term outcomes.

kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Ikizler TA et al., 2020

[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]

A prospective cohort study that examined acute kidney injury and kidney outcomes, cardiovascular events and death informs on long-term clinical outcomes.

T. Alp Ikizler, MD,[1]* Chirag R. Parikh, MD, PhD,[2]* Jonathan Himmelfarb, MD,[3]*
Vernon M Chinchilli, PhD,[4]* Kathleen D. Liu, MD, PhD,[5] Steven G. Coca, DO, MS,[6]
Amit X. Garg, MD, PhD[7] Chi-yuan Hsu, MD, MSc,[5] Edward D. Siew, MD, MSCI,[1]
Mark M. Wurfel, MD, PhD,[8] Lorraine B. Ware, MD,[9] Georgia Brown Faulkner, MS, RN,[4]
Thida C. Tan, MPH,[10] James S. Kaufman, MD,[11] Paul L. Kimmel, MD,[12] Alan S. Go, MD[5,10,13,14]*
for the ASSESS-AKI Study Investigators

[1]Division of Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN, USA

[2]Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

[3]Kidney Research Institute, Department of Medicine, University of Washington, Seattle, WA, USA

[4]Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA, USA

[5]Division of Nephrology, Department of Medicine, University of California, San Francisco School of Medicine, San Francisco, CA, USA

[6]Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[7]Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada

[8]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, WA, USA

[9]Division of Allergy, Pulmonary and Critical Care, Vanderbilt University Medical Center, Nashville, TN, USA

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

[11]Renal Section, Veterans Affairs New York Harbor Health Care System and New York University School of Medicine, New York, NY, USA

[12]Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

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

[14]Departments of Medicine (Nephrology), Health Research and Policy, Stanford University, Stanford, CA, USA

*These authors contributed equally to this work.

Corresponding author: Alan S. Go, MD

Division of Research

Kaiser Permanente Northern California

2000 Broadway

Oakland, CA 94612

Tel: 510-891-3422 / Fax: 510-891-3508

E-mail: Alan.S.Go@kp.org

Word count: 3822

Keywords: acute kidney injury, acute renal failure, chronic kidney disease, heart failure, mortality, cardiovascular disease

ABSTRACT

Acute kidney injury (AKI) has been reported to be associated with excess risks of death, kidney disease progression and cardiovascular events although previous studies have important limitations. To further examine this, we prospectively studied adults from four clinical centers surviving three months and more after hospitalization with or without AKI who were matched on center, pre-admission CKD status, and an integrated priority score based on age, prior cardiovascular disease or diabetes mellitus, preadmission estimated glomerular filtration rate (eGFR) and treatment in the intensive care unit during the index hospitalization between December 2009-February 2015, with follow-up through November 2018. All participants had assessments of kidney function before (eGFR) and at three months and annually (eGFR and proteinuria) after the index hospitalization. Associations of AKI with outcomes were examined after accounting for pre-admission and three-month post-discharge factors. Among 769 AKI (73% Stage 1, 14% Stage 2, 13% Stage 3) and 769 matched non-AKI adults, AKI was associated with higher adjusted rates of incident CKD (adjusted hazard ratio 3.98, 95% confidence interval 2.51-6.31), CKD progression (2.37,1.28-4.39), heart failure events (1.68, 1.22-2.31) and all-cause death (1.78, 1.24-2.56). AKI was not associated with major atherosclerotic cardiovascular events in multivariable analysis (0.95, 0.70-1.28). After accounting for degree of kidney function recovery and proteinuria at three months after discharge, the associations of AKI with heart failure (1.13, 0.80-1.61) and death (1.29, 0.84-1.98) were attenuated and no longer significant. Thus, assessing kidney function recovery and proteinuria status three months after AKI provides important prognostic information for long-term clinical outcomes.

INTRODUCTION

Acute kidney injury (AKI) reflects an abrupt decline in kidney function that occurs frequently among hospitalized adults and has been reported to be associated with excess risks of death, kidney disease progression and cardiovascular events.[1-8] The potential importance of AKI has been further highlighted during the coronavirus disease 2019 (COVID-19) pandemic.[9]

However, there are important limitations of many existing studies examining clinical complications after AKI. These include primarily retrospective designs that are susceptible to multiple biases, lack of systematic assessment of kidney function before and after the AKI episode, use of varying definitions of AKI, lack of adjudication of potential cardiovascular events, and inclusion of study populations with limited demographic diversity. In addition, hospitalized patients, who may be at increased risk for these events, are not always compared to similar hospitalized patients without AKI. Furthermore, the limited number of existing prospective studies have primarily focused on selected populations (e.g., coronary angiography,[10] cardiac surgery,[11-13] or myocardial infarction[14]) and have not examined heart failure separately with atherosclerotic cardiovascular events.

Given the global burden of AKI and the need for additional evidence-based clinical guidance, we addressed these issues by prospectively examining the association between AKI with subsequent kidney-related consequences, heart failure, major atherosclerotic cardiovascular events (MACE), and death among matched adults surviving a hospitalization with or without AKI. We hypothesized AKI would be independently associated with higher risks of each of these events in the presence or absence of pre-existing chronic kidney disease (CKD).

RESULTS

Baseline characteristics and follow-up

We enrolled and individually matched 769 adults with AKI and 769 adults without AKI, with 39.8% having pre-existing CKD (**Figure 1**). The distribution of matched pairs enrolled by center was 156 (20.3%) from Kaiser Permanente Northern California, 251 (32.6%) from Vanderbilt University, 154 (20.0%) from TRIBE-AKI, and 208 (27.1%) from the University of Washington (27.1%). Among AKI participants, 561 (73%), 111 (14%) and 97 (13%) had Stages 1, 2 and 3 AKI, respectively, with only 26 (1.7%) of AKI participants receiving acute renal replacement therapy. Furthermore, 48% of AKI episodes were of brief duration, 22% were of medium duration, 12% were of long duration, and 18% were of very long duration. Regardless of CKD status, compared with non-AKI participants, those with AKI were modestly younger, had slightly lower pre-admission eGFR, and were more likely to have prior cardiovascular disease, diabetes, receive care in an intensive care unit, be diagnosed with sepsis during the index hospitalization and have higher baseline study visit levels of plasma cystatin C and proteinuria. In contrast, there were no significant differences in Hispanic ethnicity, smoking status, or baseline study visit measures of body mass index, systolic or diastolic blood pressure (**Table 1**). Among participants without pre-existing CKD, the proportion of women was lower in those with AKI, but there was no significant difference in self-reported race. In participants with pre-existing CKD, there was no significant difference in gender between groups, but those with AKI were less likely to be white (**Table 1**).

Mean (SD) follow-up was 4.5 (1.8) years overall, with mean (SD) follow-up of 4.3 (1.8) years in AKI participants and 4.4 (1.8) years and non-AKI participants. During follow-up, 82 AKI and 82 non-AKI participants withdrew from the study.

Kidney outcomes

During follow-up, CKD incidence was 4.1 per 100 person-years in AKI participants compared with 1.8 per 100 person-years in matched non-AKI adults (P<0.0001) (**Figure 2A**). In participants with pre-existing CKD, the rate of those experiencing CKD progression was 2.1 per 100 person-years in AKI participants compared with 0.7 per 100 person-years in matched non-AKI participants (P<0.0001) (**Figure 2B**).

In multivariable analysis among matched participants without pre-existing CKD, AKI was associated with a 3.4-fold higher adjusted rate of incident CKD (**Model 1, Table 2**). Further adjustment for additional demographic characteristics, sepsis during the index admission and smoking, diabetes status and body mass index at the baseline visit strengthened the association (adjusted hazard ratio 3.98, 95%CI:2.51 to 6.31) (**Model 2, Table 2**). AKI was associated with a 2.3-fold higher adjusted rate of CKD progression in matched participants (**Model 1, Table 2**), and the association with CKD progression increased after adjustment for additional potential confounders (adjusted hazard ratio 2.37, 95%CI:1.28 to 4.39) (**Model 2, Table 2**). For both incident and progressive CKD, there was also a significant trend (P<0.001 for linear trend) with more severe and longer AKI in multivariable analyses (*Supplemental Appendix 2 and 3*). In a sensitivity analysis among AKI and non-AKI participants exactly matched on each matching criteria, results were similar to the main analyses (*Supplementary Appendix 4*).

Heart failure events

Among matched participants without prior CKD, the incidence of hospitalization for heart failure was higher in those with vs. without AKI (3.0 vs. 1.1 per 100 person-years, respectively, P<0.001). The pattern was similar in those with pre-existing CKD, with a higher incidence in those with vs. without AKI (5.9 vs. 3.9 per 100 person-years, respectively, P=0.014) (**Figure 2C**).

In multivariable analysis among matched participants, AKI was associated with a nearly twofold higher adjusted rate of heart failure events (**Model 1, Table 3**) that was attenuated after additional adjustment for potential confounders (adjusted hazard ratio 1.68, 95%CI:1.22 to 2.31) (**Model 2, Table 3**). However, further adjustment for eGFR, cystatin C and proteinuria measured at the 3-month post-discharge baseline visit markedly attenuated the association of AKI with subsequent heart failure hospitalization which was no longer significant (**Model 3, Table 3**). The relative strength of association was weaker in those with vs. in those without pre-existing CKD, but the patterns with multivariable adjustment were similar (**Table 3**).

In addition, after accounting for matching variables and potential confounders, there was a significant association of more severe AKI with heart failure hospitalization in those without pre-existing CKD (P=0.022 for linear trend) but not in those with pre-existing CKD (P=0.62 for linear trend). The association in those without pre-existing CKD was notably attenuated and no longer significant after further adjustment for baseline visit measures of kidney function and proteinuria (*Supplemental Appendix 2*). Longer AKI duration was associated with higher adjusted rate of heart failure hospitalization in a fully-adjusted model (*Supplemental Appendix 3*). In a sensitivity analysis of exactly matched AKI and non-AKI participants, results were similar to the main analysis except that there remained a twofold higher adjusted risk of heart failure events associated with AKI and no pre-existing CKD, even after additionally accounting for three-month post-discharge measures of kidney function and proteinuria (*Supplemental Appendix 4*).

Major atherosclerotic cardiovascular events

In those without underlying CKD, the incidence of MACE was 1.5 per 100 person-years in AKI participants compared to 1.6 per 100 person-years in matched non-AKI participants (P=0.66). There was also no significant difference in MACE incidence between those with CKD with AKI vs. without AKI (3.6 vs. 3.1 per 100 person-years, respectively, P=0.64) (**Figure 2D**).

Results were unchanged in multivariable analyses (**Table 3**). There was also no significant association between AKI severity and MACE (*Supplemental Appendix 2*). Results were similar to the main analysis in a sensitivity analysis among the subset of AKI and non-AKI participants that were exactly matched on all matching criteria (*Supplemental Appendix 4*).

Mortality

All-cause mortality was higher in those with vs. without AKI and in the presence or absence of pre-existing CKD (**Figure 2E**). After accounting for matching and additional confounders, AKI was associated with a 78% higher rate of death (**Model 2, Table 3**) that was markedly attenuated and no longer significant after further accounting for degree of renal recovery and proteinuria status at three months post-discharge (**Model 3, Table 3**). Results were similar in fully-adjusted models regardless of the presence of pre-existing CKD (**Table 3**). There was a significant trend of more severe AKI with excess mortality that was attenuated and no longer significant after adjustment for three-month post-discharge kidney function and proteinuria, while longer AKI duration was independently associated with higher mortality (*Supplemental Appendix 2 and 3*). In sensitivity analyses in the subset of AKI and non-AKI participants that were exactly matched on all matching criteria, results were similar to the main analyses, except that AKI was independently associated with a nearly twofold higher rate of death in those with pre-existing CKD even after additional adjustment for three-month post-discharge kidney function and proteinuria (*Supplemental Appendix 4*).

DISCUSSION

In a prospective cohort of matched hospital survivors, AKI was independently associated with higher subsequent risks of both incident CKD and progressive CKD. In the overall matched cohort, AKI was also associated with excess risks of heart failure hospitalization and all-cause death—regardless of the presence or absence of pre-existing CKD—but these associations

were substantially attenuated and no longer statistically significant after accounting for residual kidney function and proteinuria measured three months after discharge. In fully-adjusted models stratified by pre-existing CKD status, we also found that AKI remained significantly associated with an excess risk of heart failure events in patients without pre-existing CKD, while there was a significantly higher risk of all-cause death in those with pre-existing CKD. However, AKI was not significantly associated with MACE, overall or in those with or without pre-existing CKD.

The ASSESS-AKI Study is unique as it represents the largest prospective cohort study of a broad population of carefully-matched adults who survived at least three months after hospital discharge to examine the association of AKI with kidney and cardiovascular events over a long follow-up period. This population is highly relevant clinically as an increasingly common scenario that physicians encounter in the outpatient setting of post-hospitalization AKI survivors. Two additional key features of ASSESS-AKI compared with previous studies are the pre-specified availability of a pre-index hospitalization serum creatinine (7 to 365 days before admission) and completion of a three-month post-discharge study visit as entry criteria. The true pre-index hospitalization “baseline” serum creatinine concentration allowed us to diagnose AKI and its severity with greater precision using currently recommended criteria.[15] The systematic measurement of eGFR, plasma cystatin C and proteinuria at three months post-discharge was also critical, as we demonstrated that the overall associations of AKI with excess risks of heart failure and death were notably attenuated after accounting for residual kidney function and damage. This finding has significant clinical practice implications since evaluation of kidney function and proteinuria three months after discharge, which can be readily obtained through primary care, would yield important long-term prognostic information. Our study had several additional strengths beyond the prospective design and structured protocol among a matched cohort that helps overcome many biases that can affect retrospective studies. We had systematic, long-term follow-up measurements of post-discharge kidney function and identification and validation of heart failure events and MACE using standardized criteria. Our

cohort also included a geographically diverse set of patients recruited from ICU and non-ICU hospitalized settings.

Our study also has several limitations. Information was not available on the presence and severity of proteinuria before the index hospitalization. Data were also unavailable on pre-admission eGFR slope, as well as aetiology of the AKI episode, although we note there is no generally acceptable approach to adjudicate accurately the true aetiology of AKI.[16] Information on pre-admission blood pressure was also unavailable. Given our cohort was based in North American clinical centers and enriched with patients undergoing cardiac surgery or treated in an intensive care unit, our results may not fully generalize to all hospitalized patients, practice settings or geographic areas. As an observational study, we cannot prove causal relationships between an episode of AKI and subsequent clinical outcomes, as we cannot rule out residual or unmeasured confounding.

The population of survivors of AKI is growing in parallel with the number of patients experiencing sepsis or cardiovascular diseases, including heart failure.[17, 18] Our findings that suggest AKI, even its mildest form, may contribute to long-term adverse outcomes have important implications.[19-21] While previous studies have examined the association of AKI on kidney and cardiac complications in hospitalized patients, many suffer from several limitations. Nearly all studies were retrospective in design with their accompanying biases, and several relied only on administrative codes to assign AKI status rather than objective pre-admission and in-hospital serum creatinine results. Our study materially expands on a recent prospective study of 968 adults undergoing cardiac surgery which found that AKI was associated with a higher adjusted rate of the composite outcome of death or hospitalization for acute coronary syndrome, heart failure or receipt of coronary revascularization.[22]

Mechanisms by which AKI drives development and progression of CKD, as well as excess heart failure complications, are not fully elucidated.[23] AKI is associated with increased levels of inflammatory cytokines,[24] endothelial dysfunction,[25] dysregulation in mineral

metabolism,[26, 27] and myocardial damage.[28] Yet, shared risk factors between AKI, CKD, and cardiovascular disease (e.g., age, diabetes, hypertension) and lack of mechanistic studies have raised some skepticism about a causal relationship between AKI and future adverse outcomes.[23] One potential explanation is that the kidney plays a critical role in sodium handling and subsequent volume status and blood pressure control. Tubular injury sustained during AKI, especially in severe forms, could lead to impaired natriuresis that can predispose to subclinical vascular congestion during high sodium intake.[23, 29-31] This would, in turn, result in subtle tubular dysfunction whose effects on vulnerable kidneys may accumulate over time leading to a vicious cycle of recurrent AKI episodes, heart failure and progressive CKD.

In summary, we found that AKI independently associated with higher rates of incident and progressive CKD, as well as subsequent heart failure events and death among survivors of a recent hospitalization. However, after additionally accounting for degree of renal recovery and proteinuria status three months after discharge, the associations of AKI with heart failure and death were not significant. More severe and longer AKI duration may also be associated with worse clinical outcomes. Our study provides new data to support systematically evaluating level of kidney function recovery and proteinuria three months after an episode of AKI to provide relevant prognostic information that may help guide clinical decision-making. Furthermore, definitive randomized trial evidence is needed to determine if strategies to prevent AKI or interventions early in the course of AKI can reduce the risks of future adverse renal and cardiovascular outcomes.[23]

METHODS

Study Population

The ASSESS-AKI Study, sponsored by the National Institute of Diabetes, Digestive and Kidney Diseases of the U.S. National Institutes of Health, is a prospective, matched cohort study of hospitalized persons who did or did not experience an episode of AKI and survived to complete an in-person baseline study visit three months after discharge. Details of the design and methods have been previously described.[32] Briefly, 769 hospitalized adults who experienced an episode of AKI were enrolled between December 2009-February 2015 from four North American clinical centers involving various hospital settings (general medical and surgical wards, intensive care unit [ICU] and post-cardiac surgery), with eligibility confirmed at the baseline visit three months after discharge. Briefly, Kaiser Permanente Northern California recruited participants hospitalized in medical and surgical wards as well as ICUs at four Kaiser Permanente medical centers (Oakland, Walnut Creek, Hayward and San Francisco, CA). Vanderbilt University recruited participants from the Validation of Acute Lung Injury Biomarkers for Diagnosis (VALID) Study of critically ill patients[33] as well as patients hospitalized at Vanderbilt Medical Center (Nashville, TN) in ICU and medical and surgical ward settings. TRIBE-AKI investigators enrolled adult participants in the TRIBE-AKI (Translational Research Investigating Biomarker Endpoints for Acute Kidney Injury) Consortium[34] during pre-operative evaluation for cardiac surgery at Yale University (New Haven, CT) and London Health Sciences Center (Ontario, Canada). The University of Washington enrolled participants from the ICU as well as medical and surgical wards at Harborview Medical Center (Seattle, WA).

AKI during the index hospitalization was defined using Kidney Disease: Improving Global Outcomes (KDIGO) criteria[15] based on an increase of ≥50% or ≥0.3 mg/dL in serum creatinine concentration above an outpatient, non-emergency department baseline value within 7 to 365 days before the index admission. During the same period, a matched sample of 769 hospitalized adults without AKI at the same sites were enrolled. We aimed to have a wide range

of AKI severity represented, with targeted enrollment of one third of participants having stage 2 or 3 AKI.[15] Patients were individually matched on clinical research center and pre-admission CKD status, with additional matching to reduce confounding using an integrated, weighted priority score (0 to 100) based on prior cardiovascular disease (30 points), prior diabetes mellitus (25 points), pre-admission level of estimated glomerular filtration rate (eGFR) category (15-29, 30-44, 45-59, 60-89, 90-150 mL/min/1.73m^2) using the CKD-EPI equation[35] (20 points), age category (18-39, 40-49, 50-59, 60-69, 70-79, 80-89 years)(15 points), and receiving treatment within an intensive care unit during the index hospitalization (10 points). Detailed inclusion and exclusion criteria are described in the protocol[32] and *Supplementary Appendix 1*. Briefly, the main inclusion criteria included age 18-89 years and having a baseline outpatient, non-emergency department serum creatinine value within 365 days before enrollment. Major exclusion criteria included inability to provide consent; acute glomerulonephritis; hepatorenal syndrome; multiple myeloma, metastatic or actively treated malignancy; significant urinary tract obstruction; severe heart failure; death, receiving chronic dialysis, kidney or other transplant before the three-month post-discharge baseline visit; pregnant or breastfeeding; enrolled in an interventional study at the baseline study visit; or predicted survival of 12 months of less by a study physician.

The study was carried out in a clinical research facility. All the study participants were volunteers. Neither the study participants nor the public were involved in the development of research questions, study design and measures, or assessment of the time required to participate in the research. The study was approved by institutional review boards of the participating institutions, and written informed consent was obtained from participants. Results of the study will be shared with study participants.

Study Visits

At the three-month post-discharge baseline visit, we obtained information on sociodemographic characteristics; nephrotoxic exposures and complications occurring during the index hospitalization; cardiovascular, renal and other medical history; tobacco use; and prescription and over-the-counter medication use.[32] In addition, height, weight, blood pressure and heart rate were measured using standardized methods.[32] Blood samples for DNA, sera and plasma were collected; a urine dipstick proteinuria test performed; and 12-lead electrocardiogram was obtained using standardized methods.

A follow-up visit was conducted 12 months after the index hospitalization and annually thereafter (with determination of eGFR), with interim phone contacts at 6-month intervals.[32] Medical history, including interim hospitalizations, and medication use were updated at each contact.

Follow-up and Outcome Ascertainment

Follow-up occurred through November 2018, with censoring due to withdrawal or end of study follow-up. Vital status was updated at each study contact and through medical records review. Kidney and cardiovascular events were *a priori* considered primary outcomes.

Kidney events included incident CKD and CKD progression. Incident CKD among participants without pre-existing CKD at the index hospitalization was defined as the combination of ≥25% reduction in eGFR (compared with pre-index admission eGFR) and achieving CKD Stage 3 or worse.[36] In participants with pre-existing CKD at the index hospitalization (defined as pre-admission eGFR <60 ml/min/1.73 m^2), CKD progression was defined as ≥50% reduction in eGFR compared with baseline, reaching CKD Stage 5 or receiving renal replacement therapy (chronic dialysis or kidney transplant).[36]

We ascertained potential heart failure events and MACE based on participant self-report, and by periodic searches of electronic medical records. For all hospitalizations, we initially

obtained information on *International Classification of Diseases, Ninth or Tenth Edition* diagnostic codes for heart failure and MACE, including myocardial infarction, ischemic stroke and peripheral artery disease (codes available on request).[32] For hospitalizations without a qualifying code, the discharge summary was reviewed by a study investigator to ensure no heart failure events or MACE were missed. The event adjudication committee, comprised of trained physicians from each clinical center, centrally and locally adjudicated potential cardiovascular events based on a review of medical records using Framingham Heart Study clinical criteria[37] for heart failure and standardized criteria[38, 39] for MACE.

Vital status was captured through protocol-driven phone-based surveillance complemented by proxy reporting by participants' contacts, information from sites' electronic medical record systems, and death certificate data, as available at each participating center.

Covariates

Demographic characteristics included age, gender and self-reported race (white, black, other) and Hispanic ethnicity. We recorded self-reported tobacco use and prior cardiovascular disease (i.e., heart failure, myocardial infarction, stroke or peripheral artery disease). Hypertension was based on self-report combined with receipt of antihypertensive agents, or having a study visit systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. Diabetes mellitus was based on self-report, receipt of antidiabetic agents or glycosylated hemoglobin ≥6.5%. At the baseline visit occurring at 90 days post-discharge, we measured serum creatinine using an IDMS-traceable enzymatic assay (Roche Diagnostics, Indianapolis, IN), plasma cystatin C standardized against the international calibrator standard ERMDA471/IFCC (Gentian, Moss, Norway), and a random spot urine protein-to-creatinine ratio using a turbidimetric method (Roche, Indianapolis, IN).

Statistical approach

Analyses were conducted using SAS software, version 9.4 (Cary, NC). Characteristics were compared between matched AKI and non-AKI participants using paired t tests or Wilcoxon signed-rank tests for continuous variables and McNemar's tests for categorical variables. Rates of each outcome (per 100 person-years) with associated 95% confidence limits were calculated for AKI and non-AKI participants, and cumulative incidence curves compared using a log-rank test.

For each outcome, after confirming no violation of the proportional hazards assumption by examining log-log-survival curves, we performed nested Fine-Gray subdistribution hazard analyses[40] accounting for individual matching and competing risk of death, with additional incremental adjustment for variables not included in the matching criteria that have been previously reported or hypothesized to be risk factors for kidney and cardiovascular events, or differing between AKI and non-AKI participants at the baseline study visit. Based on an *a priori* hypothesis, pre-specified overall and stratified analyses were performed to evaluate for a potential interaction between an episode of AKI and pre-existing CKD status.[32] For cardiovascular and death outcomes, the final model additionally adjusted for three-month post-discharge measures of kidney function and proteinuria based on *a priori* hypotheses that levels of residual kidney function and damage may explain, at least in part, any observed excess risks for these clinical outcomes after an episode of AKI. Models were performed overall and stratified by pre-existing CKD status, as appropriate. Because outcomes were time-to-event with right-censoring due to death, study withdrawal or end of study follow-up, we did not impose any procedure to account for potential missingness in the outcomes.

We separately examined the association of severity of the index AKI episode with outcomes of interest by modeling KDIGO stage of AKI (1, 2 or 3) as a linear term. We used a similar approach to separately examine the association of AKI episode duration (non-AKI, AKI ≤1 day [brief], 1 day < AKI duration ≤ 3 days [medium], 3 days < AKI duration ≤ 6 days [long],

AKI duration > 6 days [very long]). Because our matching algorithm did not result in an exact match on all criteria in the 769 pairs of AKI and non-AKI participants, we also conducted sensitivity analyses among 1375 patients placed within 328 strata who were exactly matched on all individual matching criteria within each stratum.

ACKNOWLEDGEMENTS

The authors would like to thank all of the ASSESS-AKI Study participants, research coordinators and support staff for making this study possible.

The ASSESS-AKI Study Investigators are as follows (listed alphabetically): Vernon M. Chinchilli; Alan S. Go; Jonathan Himmelfarb; T. Alp Ikizler; James S. Kaufman; Paul L. Kimmel; Chirag R. Parikh; and John B. Stokes (in memoriam). Additional collaborators are as follows: Yale: Steven Coca; London, Canada: Amit Garg; Kaiser Permanente Northern California: Sijie Zheng and Leonid Pravoverov; University of California, San Francisco: Chi-yuan Hsu, Raymond K. Hsu and Kathleen D. Liu; Penn State: Nasrollah Ghahramani; University of Texas San Antonio: W. Brian Reeves; Vanderbilt: Edward D. Siew, Julia B. Lewis and Lorraine Ware; Cincinnati: Prasad Devarajan, Catherine Krawczeski, Michael Bennett; Montreal: Michael Zappitelli; Seattle: Mark Wurfel.

Support: This study was supported by the supplemental American Recovery and Reinvestment Act funds and research grants U01DK082223, U01DK082185, U01DK082192, U01DK082183, U01DK084012 and R01DK098233 from the NIDDK of the National Institutes of Health (NIH), U.S. Department of Health and Human Services. This publication was also supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH, through University of California, San Francisco–Clinical & Translational Science Institute grant UL1RR024131. Dr. Parikh is also supported by grant R01HL085757. Dr. Himmelfarb is also supported by U2CDK114886, UG3TR002158 and U01DK099923. Dr. Coca is also supported by grants R01DK106085 and U01DK106962. Dr. Garg is also supported by the Dr. Adam Linton Chair in Kidney Health Analytics, and a Clinician Investigator Award from the Canadian Institutes of Health Research. Dr. Ware is also supported by grants R01HL135849 and R01HL103836. Drs. Liu, Hsu and Go are also supported by grants

R01DK101507, U01DK060902, R01DK101507, K24DK113381 and K24DK92291. Dr. Siew is also supported by grant 5K23DK088964.

Transparency Statement: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Disclosures: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare the following: Dr. Ware has served on advisory boards for Bayer and CSL Behring and has received research funding from Boehringer Ingelheim and Global Blood Therapeutics. The remaining authors have no other relationships or activities that could appear to have influenced the submitted work. The opinions expressed in this report do not necessarily reflect those of the National Institute of Diabetes, Digestive and Kidney Diseases, the National Institutes of Health, the Department of Health and Human Services or the United States Government.

Data sharing. A complete de-identified patient data set can be made available through the NIDDK data repository.

Contributors and sources:

Contributors: TAI, CRP, JH, VMC, KDL, SGC, AXG, CYH, EDS, MMW, GBF, TCT, JSK, PLK and ASG conceived and designed the study. TAI, CRP, JH, VMC, KDL, SGC, AXG, CYH, EDS, MMW, LBW, GBF, TCT, JSK, PLK and ASG analyzed and interpreted data. TAI, VMC and ASG drafted the manuscript, and CRP, JH, KDL, SGC, AXG, CYH, EDS, MMW, LBW, GBF, TCT, JSK and PLK revised it critically for important intellectual content. All authors provided final approval of the version to be published. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ASG is the guarantor.

SUPPLEMENTARY MATERIALS

Supplemental Appendix 1. Detailed inclusion and exclusion criteria.

Supplemental Appendix 2. Severity of acute kidney injury and adverse clinical outcomes.

Supplemental Appendix 3. Category of duration of acute kidney injury and adverse clinical outcomes.

Supplemental Appendix 4. Acute kidney injury and adverse clinical outcomes in 1375 patients with and without AKI that were exactly matched on all matching criteria.

Supplementary information is available at Kidney International's website

REFERENCES

1. Mehta R, Pascual M, Soroko S*, et al.* Spectrum of acute renal failure in the intensive care unit: the PICARD experience. *Kidney Int* 2004; **66:** 1613-1621.

2. Palevsky PM, Zhang JH, O'Connor TZ*, et al.* Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; **359:** 7-20.

3. Bellomo R, Cass A, Cole L*, et al.* Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361:** 1627-1638.

4. Chawla LS, Amdur RL, Shaw AD*, et al.* Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol* 2014; **9:** 448-456.

5. James MT, Ghali WA, Knudtson ML*, et al.* Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation* 2011; **123:** 409-416.

6. Forman DE, Butler J, Wang Y*, et al.* Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *Journal of the American College of Cardiology* 2004; **43:** 61-67.

7. Go AS, Hsu CY, Yang J*, et al.* Acute Kidney Injury and Risk of Heart Failure and Atherosclerotic Events. *Clin J Am Soc Nephrol* 2018; **13:** 833-841.

8. Chalikias G, Serif L, Kikas P*, et al.* Long-term impact of acute kidney injury on prognosis in patients with acute myocardial infarction. *Int J Cardiol* 2019.

9. Batlle D, Soler MJ, Sparks MA*, et al.* Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. *J Am Soc Nephrol* 2020.

10. James MT, Samuel SM, Manning MA*, et al.* Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. *Circ Cardiovasc Interv* 2013; **6:** 37-43.

11. Hansen MK, Gammelager H, Jacobsen CJ*, et al.* Acute Kidney Injury and Long-term Risk of Cardiovascular Events After Cardiac Surgery: A Population-Based Cohort Study. *J Cardiothorac Vasc Anesth* 2015; **29:** 617-625.

12. Hansen MK, Gammelager H, Mikkelsen MM*, et al.* Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: a cohort study. *Crit Care* 2013; **17:** R292.

13. Olsson D, Sartipy U, Braunschweig F*, et al.* Acute kidney injury following coronary artery bypass surgery and long-term risk of heart failure. *Circ Heart Fail* 2013; **6:** 83-90.

14. Parikh CR, Coca SG, Wang Y*, et al.* Long-term prognosis of acute kidney injury after acute myocardial infarction. *Arch Intern Med* 2008; **168:** 987-995.

15. Kidney Disease: Improving Global Outcomes (KDIGO) Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kid International* 2012; **Suppl 2:** 1-138.

16. Koyner JL, Garg AX, Thiessen-Philbrook H*, et al.* Adjudication of etiology of acute kidney injury: experience from the TRIBE-AKI multi-center study. *BMC Nephrol* 2014; **15:** 105.

17. Hsu CY. Where is the epidemic in kidney disease? *Journal of the American Society of Nephrology : JASN* 2010; **21:** 1607-1611.

18. Benjamin EJ, Muntner P, Alonso A*, et al.* Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019; **139:** e56-e528.

19. Heywood JT, Fonarow GC, Costanzo MR*, et al.* High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007; **13:** 422-430.

20. Fonarow GC, Adams KF, Jr., Abraham WT*, et al.* Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *Jama* 2005; **293:** 572-580.

21. Forman DE, Butler J, Wang Y*, et al.* Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *Journal of the American College of Cardiology* 2004; **43:** 61-67.

22. Parikh CR, Puthumana J, Shlipak MG*, et al.* Relationship of Kidney Injury Biomarkers with Long-Term Cardiovascular Outcomes after Cardiac Surgery. *J Am Soc Nephrol* 2017; **28:** 3699-3707.

23. Chawla LS, Eggers PW, Star RA*, et al.* Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; **371:** 58-66.

24. Hoke TS, Douglas IS, Klein CL*, et al.* Acute renal failure after bilateral nephrectomy is associated with cytokine-mediated pulmonary injury. *Journal of the American Society of Nephrology* 2007; **18:** 155-164.

25. Ko GJ, Grigoryev DN, Linfert D*, et al.* Transcriptional analysis of kidneys during repair from AKI reveals possible roles for NGAL and KIM-1 as biomarkers of AKI-to-CKD transition. *American journal of physiology Renal physiology* 2010; **298:** F1472-1483.

26. Christov M, Waikar SS, Pereira RC*, et al.* Plasma FGF23 levels increase rapidly after acute kidney injury. *Kidney International* 2013; **84:** 776-785.

27. Leaf DE, Waikar SS, Wolf M*, et al.* Dysregulated mineral metabolism in patients with acute kidney injury and risk of adverse outcomes. *Clin Endocrinol (Oxf)* 2013; **79:** 491-498.

28. Song D, de Zoysa JR, Ng A*, et al.* Troponins in acute kidney injury. *Ren Fail* 2012; **34:** 35-39.

29. Basile DP, Donohoe D, Roethe K*, et al.* Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. *American journal of physiology Renal physiology* 2001; **281:** F887-899.

30. Basile DP, Leonard EC, Tonade D*, et al.* Distinct effects on long-term function of injured and contralateral kidneys following unilateral renal ischemia-reperfusion. *American journal of physiology Renal physiology* 2012; **302:** F625-635.

31. Pechman KR, De Miguel C, Lund H*, et al.* Recovery from renal ischemia-reperfusion injury is associated with altered renal hemodynamics, blunted pressure natriuresis, and sodium-sensitive hypertension. *Am J Physiol Regul Integr Comp Physiol* 2009; **297:** R1358-1363.

32. Go AS, Parikh CR, Ikizler TA*, et al.* The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. *BMC Nephrol* 2010; **11:** 22.

33. Siew ED, Ware LB, Gebretsadik T*, et al.* Urine neutrophil gelatinase-associated lipocalin moderately predicts acute kidney injury in critically ill adults. *J Am Soc Nephrol* 2009; **20:** 1823-1832.

34. Parikh CR, Coca SG, Thiessen-Philbrook H*, et al.* Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. *J Am Soc Nephrol* 2011; **22:** 1748-1757.

35. Levey AS, Stevens LA, Schmid CH*, et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604-612.

36. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney international* 2013; **Suppl:** 1-150.

37. McKee PA, Castelli WP, McNamara PM*, et al.* The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285:** 1441-1446.

38. Thygesen K, Alpert JS, Jaffe AS*, et al.* Third universal definition of myocardial infarction. *Journal of the American College of Cardiology* 2012; **60:** 1581-1598.

39. Hicks KA, Tcheng JE, Bozkurt B*, et al.* 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Journal of the American College of Cardiology* 2015; **66:** 403-469.

40. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94:** 496-509.

TABLES

Table 1. Baseline characteristics of adults with and without acute kidney injury, stratified by the presence or absence of chronic kidney disease at study entry.

Characteristic	No Pre-Existing CKD			Pre-Existing CKD		
	Acute Kidney Injury (N=463)	No Acute Kidney Injury (N=463)	P Value	Acute Kidney Injury (N=306)	No Acute Kidney Injury (N=306)	P Value
Serum creatinine, mg/dL						
Pre-admission	0.94 (0.20)	0.87 (0.17)	<0.0001	1.69 (0.60)	1.47 (0.48)	<0.0001
Inpatient	2.14 (1.71)	0.90 (0.20)	<0.0001	2.94 (1.76)	1.43 (0.44)	<0.0001
3-month baseline	1.02 (0.47)	0.86 (0.20)	<0.0001	1.71 (0.78)	1.37 (0.50)	<0.0001
Estimated GFR, ml/min/1.73 m^2 – mean (SD)						
Pre-admission	83.8 (17.8)	86.1 (16.1)	0.003	42.0 (12.1)	46.0 (10.2)	<0.0001
Inpatient	41.6 (17.2)	84.0 (17.5)	<0.0001	24.3 (9.6)	47.7 (12.3)	<0.0001
3-month baseline	79.8 (22.5)	86.9 (17.9)	<0.0001	44.3 (17.3)	51.2 (14.7)	<0.0001
Mean (SD) age, yr	60.7 (12.9)	61.7 (13.1)	0.02	68.1 (11.2)	71.1 (9.4)	<0.0001
Women – no. (%)	129 (27.9)	191 (41.3)	<0.0001	121 (39.5)	133 (43.5)	0.39
Race – no. (%)			0.27			0.02
White	378 (81.6)	394 (85.1)		229 (74.8)	259 (84.6)	
Black	65 (14.0)	47 (10.1)		52 (17.0)	31 (10.1)	
Other	20 (4.4)	22 (4.8)		25 (8.2)	16 (5.3)	
Hispanic ethnicity – no. (%)	13 (2.8)	10 (2.2)	0.68	8 (2.6)	7 (2.3)	0.99
Smoking status – no. (%)			0.10			0.48
Never	176 (38.0)	209 (45.1)		132 (43.1)	117 (38.2)	
Former	199 (43.0)	188 (40.6)		145 (47.4)	157 (51.3)	
Current	87 (18.8)	61 (13.2)		25 (8.2)	29 (9.5)	
Unknown	1 (0.2)	5 (1.1)		4 (1.3)	3 (1.0)	
Prior cardiovascular disease – no. (%)	200 (43.2)	147 (31.8)	<0.0001	172 (56.2)	146 (47.7)	<0.0001
Prior diabetes mellitus – no. (%)	201 (43.4)	147 (31.8)	<0.0001	186 (60.8)	127 (41.5)	<0.0001
Treated in ICU during index admission – no. (%)	340 (73.4)	307 (66.3)	<0.0001	205 (67.0)	166 (54.2)	<0.0001
Sepsis during index admission – no. (%)	89 (19.2)	14 (3.0)	<0.0001	29 (9.5)	12 (3.9)	0.006
3-month baseline measurements – mean (SD)						
Body mass index, kg/m^2 - mean (SD)	31.4 (8.5)	30.5 (7.2)	0.07	32.0 (8.1)	30.6 (6.8)	0.07
Systolic blood pressure, mmHg – mean (SD)	128 (22)	126 (19)	0.27	129 (23)	127 (20)	0.36
Diastolic blood pressure, mmHg – mean (SD)	73 (13)	74 (13)	0.42	68 (14)	69 (14)	0.55
Plasma cystatin C, mg/L - median (IQR)	1.2 (1.0, 1.5)	1.0 (0.9, 1.2)	<0.0001	2.0 (1.6, 2.6)	1.7 (1.4, 1.9)	<0.0001
Urine protein-to-creatinine ratio - median (IQR)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.03	0.2 (0.1, 0.7)	0.1 (0.1, 0.3)	<0.0001

Table 2. Association of acute kidney injury with development of incident chronic kidney disease and progression of chronic kidney disease.

Nested Model	Hazard Ratio (95% Confidence Interval) of AKI vs. No AKI on Kidney Outcomes	
	Incident Chronic Kidney Disease	**Chronic Kidney Disease Progression**
Model 1: Matched* cohort	3.41 (2.35 to 4.95)	2.30 (1.32 to 3.99)
Model 2: Model 1 + gender; race/ethnicity; sepsis during index admission; 3-month baseline visit smoking status, diabetes status and body mass index	3.98 (2.51 to 6.31)	2.37 (1.28 to 4.39)

*Matching variables included Clinical Center, age, pre-index admission estimated glomerular filtration rate, pre-index admission diabetes status, prior cardiovascular disease, and intensive care unit stay during index admission

Table 3. Association of acute kidney injury with subsequent heart failure, major atherosclerotic cardiovascular events and death, overall and stratified by pre-existing chronic kidney disease.

	Hazard Ratio (95% Confidence Interval) of AKI vs. No AKI								
	Heart Failure			Major Atherosclerotic Cardiovascular Event			Death from Any Cause		
Nested Model	**Overall**	**No Pre-existing CKD***	**Pre-existing CKD**	**Overall**	**No Pre-existing CKD**	**Pre-existing CKD**	**Overall**	**No Pre-existing CKD**	**Pre-existing CKD**
Model 1: Matched† cohort	1.83 (1.37 to 2.44)	2.70 (1.73 to 4.21)	1.24 (0.89 to 1.72)	1.01 (0.**75** to 1.34)	0.95 (0.64 to 1.40)	1.07 (0.73 to 1.56)	1.89 (1.35 to 2.63)	1.67 (1.08 to 2.58)	2.13 (1.36 to 3.34)
Model 2: Model 1 + gender, race/ethnicity, sepsis during index admission, 3-month baseline visit smoking status, diabetes status and body mass index	1.68 (1.22 to 2.31)	2.47 (1.54 to 3.96)	1.14 (0.79 to 1.66)	0.95 (0.70 to 1.28)	0.90 (0.59 to 1.37)	1.00 (0.65 to 1.52)	1.78 (1.24 to 2.56)	1.38 (0.85 to 2.26)	2.29 (1.41 to 3.71)
Model 3: Model 2 + 3-month baseline visit estimated glomerular filtration rate, plasma cystatin C and urine protein-to-creatinine ratio	1.13 (0.80 to 1.61)	1.48 (0.94 to 2.33)	0.87 (0.55 to 1.38)	1.20 (0.85 to 1.70)	0.99 (0.63 to 1.55)	1.46 (0.92 to 2.30)	1.29 (0.84 to 1.98)	1.34 (0.75 to 2.39)	1.24 (0.70 to 2.18)

*CKD denotes chronic kidney disease

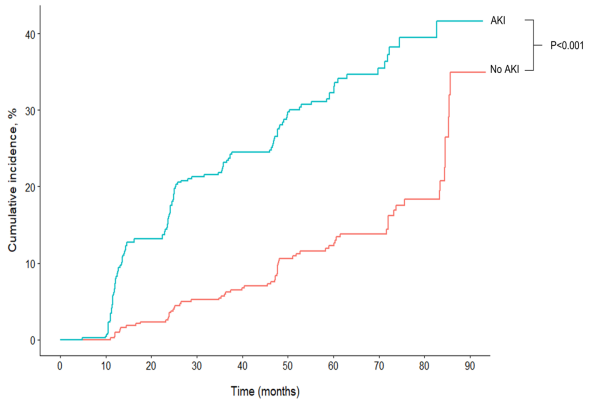
†Matching variables included Clinical Center, age, pre-index admission estimated glomerular filtration rate, pre-index admission diabetes status, prior cardiovascular disease, and intensive care unit stay during index admission.

FIGURE LEGENDS

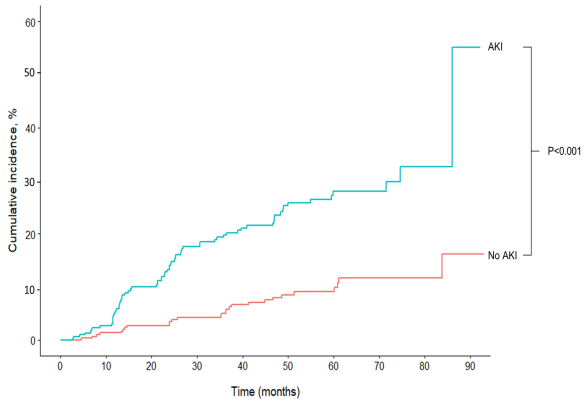
Figure 1. Assembly of matched cohort of adults surviving a hospitalization with and without acute kidney injury.

Figure 2. Kaplan-Meier estimates of renal, major atherosclerotic cardiovascular events, heart failure events and all-cause death in patients with and without acute kidney injury, stratified by the presence or absence of pre-existing chronic kidney disease. Panel A shows results for incident chronic kidney disease. Panel B shows results for progressive chronic kidney disease. Panel C shows results for major atherosclerotic events. Panel D shows results for heart failure events. Panel E shows results for all-cause death.

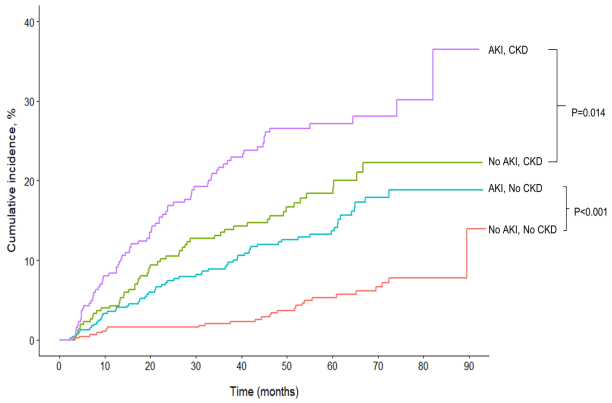
A. Chronic Kidney Disease Incidence



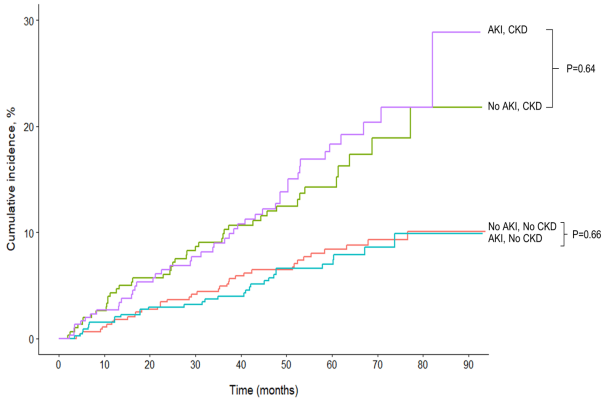
B. Chronic Kidney Disease Progression



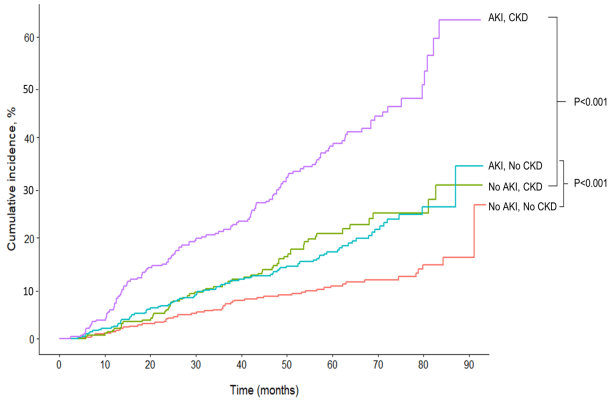
C. Heart Failure

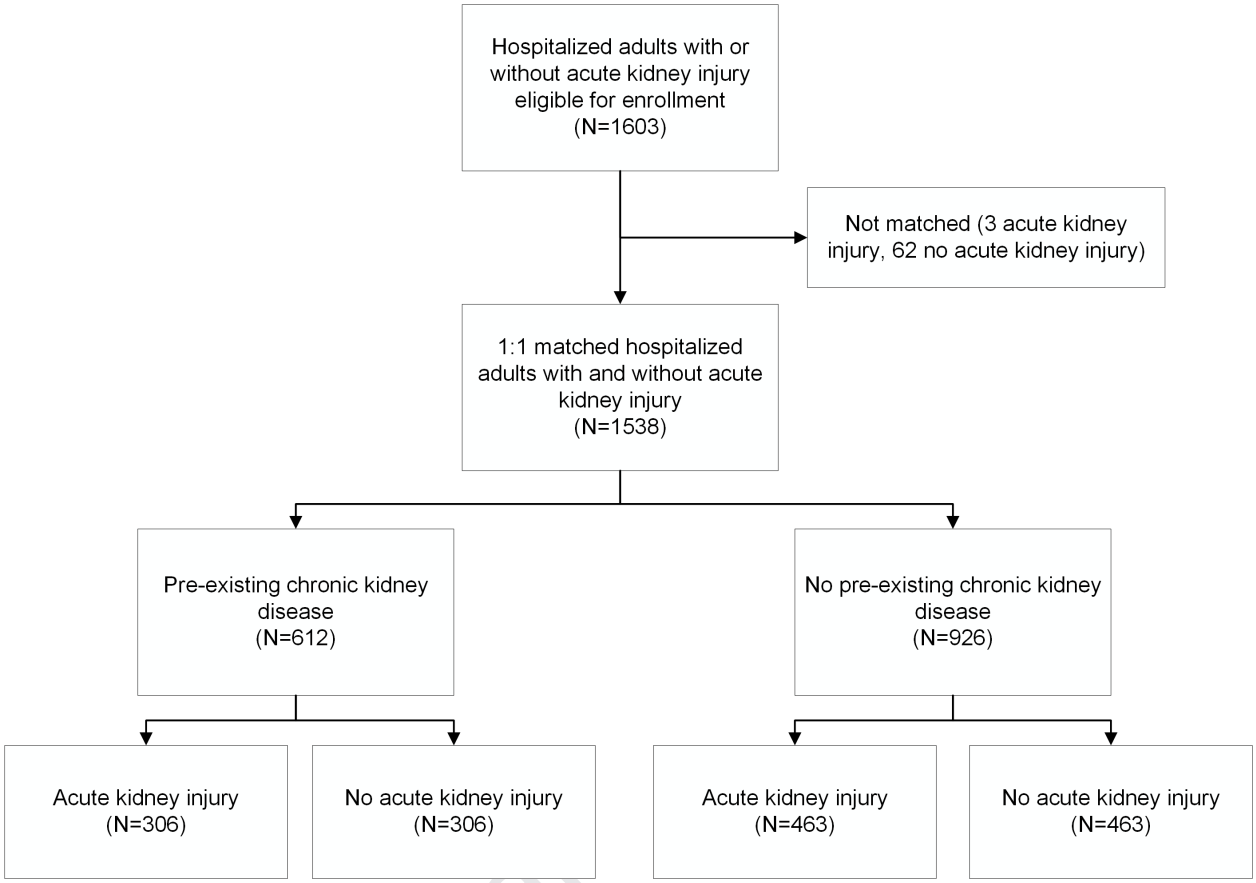


D. Major Adverse Cardiovascular Events



E. Death




Hospitalized adults with or without acute kidney injury eligible for enrollment (N=1603)
Not matched (3 acute kidney injury, 62 no acute kidney injury)
1:1 matched hospitalized adults with and without acute kidney injury (N=1538)
Pre-existing chronic kidney disease (N=612)
No pre-existing chronic kidney disease (N=926)
Acute kidney injury (N=306)
No acute kidney injury (N=306)
Acute kidney injury (N=463)
No acute kidney injury (N=463)