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Risk of chronic kidney disease progression after acute kidney injury: findings from the Chronic Renal Insufficiency Cohort (CRIC) study

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Abstract

Background: Prior studies associating AKI with more rapid subsequent loss of kidney function have methodological limitations, including inadequate control for differences between those who did and did not experience AKI.

Objective: To determine whether AKI is independently associated with subsequent kidney function trajectory among patients with CKD.

Design, Setting, Patients: Multicenter prospective U.S. cohort of patients with CKD (N=3150).

Measurements: Hospitalized AKI was defined by a ≥50% nadir to peak inpatient serum creatinine (SCr) increase. Kidney function trajectory was assessed using estimated glomerular filtration rate (eGFR) based on SCr (eGFRcr) or cystatin C (eGFRcys) measured at annual research study visits.

Results: During a median follow-up of 3.9 years, 433 CRIC study participants experienced at least one episode of AKI. Most AKI episodes (92%) were stage 1 or 2 in severity. There was a drop in eGFRcr (−2.30 ml/min/1.73m^2 (95%CI −3.70, −0.86)) and eGFRcys (−3.61 ml/min/1.73m^2 (95%CI −6.39, −0.82)) after AKI. However, in fully adjusted models, the drops were attenuated to −0.38 ml/min/1.73m^2 (95%CI −1.35, 0.59) for eGFRcr and −0.15 ml/min/1.73m^2 (95%CI −2.16, 1.86) for eGFRcys and the confidence interval bounds included the possibility of no effect. Estimates of changes in eGFR slope after AKI determined by either SCr (0.04 ml/min/1.73m^2/year (95%CI −0.30, 0.38)) or cystatin C (−0.56 ml/min/1.73m^2/year (95%CI −1.28, 0.17)) also had confidence interval bounds which included the possibility of no effect.

Limitations: Few cases of severe AKI no adjudication of AKI cause, lack of information regarding nephrotoxic exposures after hospital discharge.

Conclusion: After accounting for pre-AKI eGFR, proteinuria and other co-variables the association between mild to moderate AKI and worsening subsequent kidney function in patients with CKD is small.

INTRODUCTION

Many have come to accept that acute kidney injury (AKI), previously considered a short-term, limited and entirely reversible condition, is an independent risk factor for accelerated loss of kidney function (1–3). This has led to changes in research focus, practice patterns and public health targets. For example, clinical trials were launched to test if reducing AKI risk will lower rates of subsequent persistent impairment in kidney function (4, 5). In England, hospitals have been financially incentivized to restructure discharge care following AKI, including more frequent blood tests (6). And the U.S. Health People 2030 has as an objective to increase the proportion of Medicare beneficiaries who have kidney function evaluated 3 months after AKI hospitalization (7).

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However, studies associating AKI with more rapid subsequent loss of kidney function have methodological limitations, including inadequate control for differences between those who did and did not experience AKI (8–10). For example, one study reported that an acute 0.1 mg/dl change in serum creatinine was associated with a 45% increase in future risk of end-stage kidney disease (ESKD) (11), which seems to be an implausible effect size. We hypothesize that the observed association between an episode of AKI and more rapid subsequent loss of renal function will be considerably attenuated after control for pre-AKI estimated glomerular filtration rate (eGFR), pre-AKI proteinuria and pre-AKI eGFR slope (10). This is because low eGFR and higher proteinuria are strong risk factors for both AKI and CKD progression (12). Patients with AKI may also already have more rapid rates of eGFR loss pre-hospitalization compared with patients without AKI (13). Few prior studies, however, have systematically accounted for these. A more refined understanding of the independent association of AKI and change in kidney function trajectory may lead to better tailored clinical guidelines for post-AKI care.

To fill these gaps in the literature, we leveraged the multicenter prospective Chronic Renal Insufficiency Cohort (CRIC) study (14, 15) and analyzed serum creatinine (SCr), cystatin C and proteinuria repeatedly measured at a fixed frequency determined by research protocol before and after an AKI episode.

METHODS

Study population

The CRIC study is a multicenter prospective cohort study of racially and ethnically diverse adults with CKD in the U.S (14, 15). The present analysis included CRIC study participants who were alive, not withdrawn from the study and did not develop ESKD by July 1, 2013 (Figure 1). We selected July 1, 2013, as the start date for this analysis since we rely on changes in SCr levels during hospitalization to define AKI, and CRIC started comprehensive collection of inpatient laboratory measurements only after July 1, 2013.

CRIC participants are contacted every six months by phone and attend annual in-person research study visits during which SCr, cystatin C and urine protein-creatinine ratio (uPCR) are measured, and vital signs, medication usage and interim medical events are comprehensively updated. For the purposes of this study, “baseline” visit refers to the first in-person visit after July 1, 2013, with SCr-based eGFR measurement. Follow-up was through December 27th, 2018.

Institutional review boards at participating institutions approved the study protocol. All study participants provided written informed consent.

Outcome of eGFR and estimands

The primary outcome of interest was eGFR. The estimands (parameters of interest) were change in absolute eGFR value and change in eGFR slope before vs. after an episode of hospitalized AKI (Supplementary Figure 1).

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We used protocol-driven CRIC in-person annual study visit measurements to calculate eGFR based on either the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) SCr equation (16) or the 2012 CKD cystatin C equation (17). All CRIC SCr measurements were calibrated to isotope-dilution mass spectrometry-traceable standards (18). A cystatin C standardization was implemented in CRIC internally to correct for drift over time (19).

Hospitalized AKI

Hospitalizations among CRIC participants were ascertained at annual study site visits and interim 6-month telephone calls, along with study personnel review of hospital discharge records collected by active surveillance. SCr values measured during all hospitalizations were systematically abstracted to determine AKI status (20).

Hospitalized AKI (hereafter referred to as AKI) was defined by a ≥50% increase from nadir to peak inpatient SCr measurement. This definition is adapted from the Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines (21), but is more stringent to improve specificity and reduce false positives (22). AKI was classified as stage 2 if the peak-nadir SCr ratio was ≥2 and stage 3 if the peak-nadir SCr ratio was ≥3; all others were classified as stage 1.

The main exposure was the time-updated cumulative episodes of AKI. The time-updated cumulative episodes of AKI started as 0 at the first in-person annual CRIC study visit after July 1, 2013 and increased by 1 at the following annual visit after any episodes of AKI. Multiple AKI episodes occurring between two consecutive in-person CRIC annual study visits were categorized as a single episode. We chose this approach because there were not that many instances when more than one episode of AKI occurred between annual study visits and because we did not have outpatient SCr measurements (which were only collected at the annual visit) to assess the association of each individual AKI episode occurring in between annual visit with outcomes. In a sensitivity analysis, we counted all episodes of AKI regardless of timing relative to CRIC study visits.

We used only CRIC in-person study visit SCr measurements to define CKD trajectory (outcome) and only inpatient SCr measurements to define AKI (exposure).

Covariates

Demographic characteristics included age, sex and self-reported race/ethnicity (non-Hispanic Black, non-Hispanic White, Hispanic or other). Diabetes mellitus (diabetes), heart failure, systolic blood pressure, receipt of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) were assessed biannually and incorporated as time-updated variables in analyses. Diabetes was defined as either fasting glucose ≥7 mmol/L (126 mg/dl), random glucose ≥11.1 mmol/L (200 mg/dl), or self-reported use of insulin or oral diabetic medication (23). Heart failure was identified from self-report and adjudicated from hospitalization and emergency department medical records (24). Blood pressure was measured via a standardized protocol (25), using a Tycos Classic Hand Aneroid cuff and sphygmomanometer (Welch Allyn) from study inception to 2018 and then since 2018 using an oscillometric device, Omron HEM907-XL.

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At annual study visits, along with SCr, cystatin C and uPCR were quantified (using either 24-hour urine collections or random spot urine samples) (26).

Statistical analysis

Initially, descriptive statistics were used to characterize the study population.

We then used linear mixed effects regression models to examine the associations of AKI with eGFR decline (Supplementary Figure 1). There was no imputation for missing data which were handled by the mixed effects regression models under the missing at random assumption. The linear mixed effects regression models included time-updated cumulative hospitalizations, time-updated cumulative episodes of AKI, years of follow-up, an interaction term between time-updated cumulative hospitalizations and years of follow-up, and an interaction term between time-updated cumulative episodes of AKI and years of follow-up as fixed effects and participants and slope of years of follow-up as random effects. Given that most participants did not have more than one episode of AKI across multiple years, we considered each episode of AKI to have an independent and additive effect (see form of mixed-effect model in Supplementary Figure 1 legend).

The following covariates were sequentially adjusted for, in serial models: 1) clinical center and demographic characteristics (age, sex, and race/ethnicity); 2) additional adjustment for time-updated diabetes, heart failure, systolic blood pressure, receipt of ACEi and ARBs; and 3) additional adjustment for (log transformed) uPCR; 4) additional adjustment for baseline eGFR (that was measured at the first in-person annual CRIC study visit after July 1, 2013). The presences of diabetes and heart failure are carried forward i.e., once a participant is identified as having diabetes or heart failure, the statuses remain present for the rest of the follow-up. Receipt of ACEi and ARBs and systolic blood pressure are not carried forward, instead, we used assessments at each CRIC study visit to determine whether participants were on these medications and what their systolic blood pressures were. To reflect the associations between covariates and eGFR, the interactions between covariates and years of follow-up were also included in the linear mixed effects regression models. To report estimated eGFR slope for one episode of AKI, the average values of covariates at baseline were entered in the model as an average person.

We performed exploratory analyses examining the impact of different stages of AKI defined using consensus definitions (21) and AKI of different duration (<3 vs. ≥3 days). We defined duration of AKI based on if SCr readings continued to remain elevated ≥50% above nadir inpatient SCr measurement. We reasoned that pre-renal azotemia and uncomplicated urinary obstruction should be readily reversible and thus not last 3 or more days. In these analyses, the time-updated cumulative episodes of AKI increased by 1 at the following annual visit only after an episode of AKI subtype of interest. We performed analyses stratified by baseline eGFR above or below 45 ml/min/1.73m^2 (cutoff for stage 3a vs. 3b CKD) and baseline proteinuria above or below median (uPCR 0.13 g/g). We also categorized AKI as those occurring during heart-failure related hospitalizations (using previously reported heart-failure adjudication in the CRIC study (27)) or AKI occurring during infection-related hospitalizations or during cardiovascular-related hospitalizations (defined using the Clinical Classifications Software (CCS) as previously reported (20, 28)).

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Analyses were performed using SAS/STAT software, Version 9.4 of the SAS System for Windows (Copyright © 2016 SAS Institute Inc., Cary, NC, USA).

Role of the funding source

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RESULTS

We included a total of 3,150 study participants, of whom 44% were female, and 43% self-identified as non-Hispanic Black. The mean (SD) baseline age was 65 (9) years, 54% had diabetes, and 11% had a history of heart failure. At baseline, the mean eGFR based on SCr (eGFRcr) was 52 (17) ml/min/1.73m^2, mean eGFR based on cystatin C (eGFRcys) was 51 (21) ml/min/1.73m^2 and median uPCR was 0.13 g/g (IQR 0.06–0.47) (Table 1).

Among individuals who were hospitalized during the study period (N=1837), pre-hospitalization eGFR slope was steeper (i.e., more negative), pre-hospitalization uPCR level was greater and baseline eGFR was lower among those who had AKI (N= 433) compared with those who did not (N=1399) (Table 1).

A total of 612 episodes of AKI were observed among 433 participants during a median follow-up of 3.9 years. Most AKI episodes were stage 1 or 2 in severity (68% and 24% respectively). 153 out of 612 (25%) of the AKI episodes were 3 days or longer. Among the 433 participants with AKI, 320 (74%) had only one AKI episode, although 15 (3%) had four or more AKI episodes if all episodes were tallied regardless of timing relative to CRIC study visit. However, our main mixed effects model considered multiple AKI episodes occurring between two consecutive annual CRIC study visits as a single episode (see form of mixed-effect model in Supplementary Figure 1 legend), in which case 62 (14.3%) study participants were considered to have two AKI episodes and 7 participants (1.6%) were considered to have three or more AKI episodes.

Among those with at least 1 AKI episode (n = 433), mean (SD) number of SCr measurements before the first episode of AKI was 2.2 (1.1) and mean (SD) number after the first episode of AKI was 2.4 (1.2). Mean (SD) number of cystatin C measurements before the first episode of AKI was 2.1 (1.0) and mean (SD) number after the first episode of AKI was 2.0 (1.1).

Change in eGFRcr and eGFRcys after AKI

In an unadjusted linear mixed effects regression model, each episode of AKI was associated with an absolute change in eGFRcr of −2.30 (95 % CI: −3.70, −0.86) ml/min/1.73 m^2 and eGFRcys of −3.61 ml/min/1.73m^2 (95%CI −6.39, −0.82)) (Table 2 and 3 unadjusted model). This estimated drop in eGFR was similar after controlling for clinical center and demographic characteristics (Table 2 and 3 Model 1) but was attenuated after further adjusting for time-updated diabetes, heart failure, systolic blood pressure, and receipt of ACEi and ARBs (Table 2 and 3 Model 2). Additional adjustment for uPCR and baseline

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eGFR further attenuated the association such that the confidence interval bounds included the possibility of no effect: −0.38 (−1.35, 0.59) ml/min/1.73 m^2 for eGFRcr and −0.15 ml/min/1.73m^2 (95%CI −2.16, 1.86) for eGFRcys (Table 2 and 3 Model 4).

Change in eGFRcr and eGFRcys slope after AKI

In our fully adjusted model (Table 2 and 3 Model 4), estimates of changes in eGFR slope after AKI determined by either SCr (0.04 ml/min/1.73m^2/year (95%CI −0.30, 0.38)) or cystatin C (−0.56 ml/min/1.73m^2/year (95%CI −1.28, 0.17)) also had confidence interval bounds which included the possibility of no effect.

Exploratory analyses

Compared with our main analysis which categorized multiple AKI episodes occurring between two consecutive in-person CRIC annual study visits as a single episode, very similar results were seen in the sensitivity analysis which counted all AKIs regardless of timing relative to CRIC study visits (Supplementary Table 1).

The results separating out stage 1, stage 2 and stage 3 AKI episodes are shown in Supplementary Table 2.

Supplementary Table 3 shows the results for AKI episode of <3 vs. ≥3 days duration. Results from stratified analyses by higher and lower levels of baseline eGFR and proteinuria are shown in Supplementary Tables 4 and 5. Supplementary Table 6 shows the results of AKI occurring in subtypes of hospitalizations. AKI was not consistently predictive of more rapidly subsequent loss of kidney function by both eGFRcr and eGFRcys in any of these additional analyses.

DISCUSSION

In this study, we found that after accounting for patient characteristics such as prehospitalization levels of eGFR slope and proteinuria, AKI did not predict worsening of subsequent kidney function trajectory. The parameter estimates and confidence intervals indicate that any independent association between mild to moderate AKI and more rapid subsequent CKD progression would be small.

We believe this prospective study provides more rigorous and less biased estimates than prior reports. Our approach using linear mixed effects regression models leveraging an existing prospective cohort study has several advantages. First, it accommodates the fact that AKI can occur at various points during follow-up; therefore, the number of pre-AKI and post-AKI SCr or cystatin C measurements vary. Second, it shifts emphasis away from comparing eGFR values post-hospitalization for those who did and did not experience AKI. Rather, the primary comparison is within each individual, thus, accounting for that person’s own pre-AKI eGFR slope. Third, the mixed effects model was able to handle other important time-updated covariates such as each person’s own pre-AKI uPCR. Fourth, we accounted for hemodynamic factors which may affect eGFR level, such as subsequent use of renin-angiotensin-system blockers or more intensive blood pressure control. Cessation of renin-angiotensin-system blockers and less intense blood pressure control immediately

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after the AKI episode and may be reasons why prior some studies showed that AKI was associated (unexpectedly) with increased eGFR (29), which complicates interpretation of the subsequent eGFR slope. Fifth, the mixed effects model allowed for multiple episodes of AKI during follow up. Sixth, analyzing data collected as part of a research protocol greatly reduces missing data and ascertainment bias. In contrast, in studies relying on routine clinical data, those who had AKI may have more SCr measurements after hospital discharge, thus increasing the opportunity to ascertain development or worsening of CKD (10, 30).

In contrast with our findings, studies by James (31), Asar (32), D'Hoore (33) and Jensen (34) have reported that AKI was associated with more rapid subsequent loss of eGFRcr. Hapca et al. compared the change in eGFR slope from before to after an AKI episode in a Scottish population and found no statistically significant worsening of eGFR slope among those with CKD (regardless of diabetes status) or among those with diabetes and without CKD (13). Among those without diabetes and without CKD, the eGFR slope was steeper ($p=0.038$) after AKI (13) by −0.55 mL/min/1.73 m^2/year. However, none of these studies had systematic ascertainment of proteinuria prior to AKI and all analyzed data collected as part of routine clinical care.

There are only two other prospective cohort studies we are aware of which ascertained kidney function trajectory after AKI systematically according to a research protocol--Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) (35) and AKI Risk in Derby (ARID) (36). An advantage of CRIC over ASSESS-AKI and ARID is the availability of information on proteinuria level and GFR slope before the index AKI episode. In addition, we estimated GFR using both SCr and cystatin C which has not been done in prior studies. This addresses concerns that the magnitude of kidney function loss after AKI (37–39) may be underestimated by artifactually lower SCr concentrations due to decreased muscle-mass and creatinine production following AKI hospitalizations with longer length of stay, a factor which should not affect cystatin C (40–45).

Our results suggest that much of the kidney disease observed post-AKI may already be present prior to AKI. Thus, efforts focused at ameliorating the effects of the AKI episode (46, 47) may have only a small impact on overall burden of CKD. A better strategy may be to focus on flattening eGFR slope and treating proteinuria before the AKI episode. But a diagnosis AKI does present an opportunity to identify high risk patients and implement evidence-based interventions to slow down CKD progression.

Showing that the independent association between mild to moderate AKI and subsequent worsening of CKD is very modest in magnitude (e.g., as estimated by the 95% confidence intervals in Tables 2 and 3) fits well with results from existing randomized clinical trials of interventions reporting that reducing AKI rates did not diminish subsequent CKD risks (5, 48). In those randomized trials, the rates of AKI were not high and were only modestly reduced by the interventions (5, 48), so it is not surprising that CKD risks were not lower in the interventional arms (5, 48).

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Additional strengths of this study include defining AKI using observed acute changes in SCr rather than administrative codes which are known to have suboptimal performance characteristics (49, 50). We clearly separated inpatient, clinically obtained SCr values used to ascertain AKI from outpatient, research study visit obtained SCr values used to determine pre- and post-AKI eGFR slope. Otherwise, it might have been challenging to distinguish occurrence of AKI from rapid progression of CKD (8, 13, 51). Our study population was not limited to specialized patient populations such as those undergoing cardiac catheterization (31) or coronary artery bypass surgery (52).

Limitations of this study include lack of details around the AKI events including the nature of the nephrotoxic insult(s) leading to AKI--a shortcoming shared by many other AKI epidemiology studies. We did not adjudicate causes of AKI but there is no accepted gold-standard methodology to adjudicate AKI etiology (including how to reliably distinguish between prerenal azotemia and acute tubular necrosis (ATN)(53)) and prior studies have shown poor agreement across adjudicators (54). But it is possible that one would be able to better predict loss of renal function after AKI with more refined understanding of AKI etiologies. The unexpected finding of large improvement in eGFRcr (but not eGFRcys) after AKI episodes occurring during infection-related hospitalizations is not easy to explain. But this is a very heterogeneous category (as indicated by footnote in Supplementary Table 6) and there are data suggesting that sepsis is associated with reduced creatinine generation (55, 56) which would lead to artifactually higher eGFRcr. We did not have information on use (or avoidance) of nephrotoxic medications after AKI which may have impacted subsequent eGFR values. Most of the AKI cases in CRIC were mild to moderate in severity and we thus had limited power to assess the impact of more severe AKI on post-AKI eGFR values. A previous study by Amdur et al. (57) reported that there was a ~10 mL/min/1.73 m^2 fall in eGFRcr comparing values obtained in the year before vs. the year after hospitalization among hospitalized U.S. veterans with ATN, of whom three-quarters had stage 3 AKI. All CRIC participants had CKD and were research volunteers so our results may not generalize to other populations.

In conclusion, this study more rigorously addressed methodological limitations presented in prior published studies to conclude that the independent association between mild to moderate AKI and worsening subsequent kidney function trajectory appears small.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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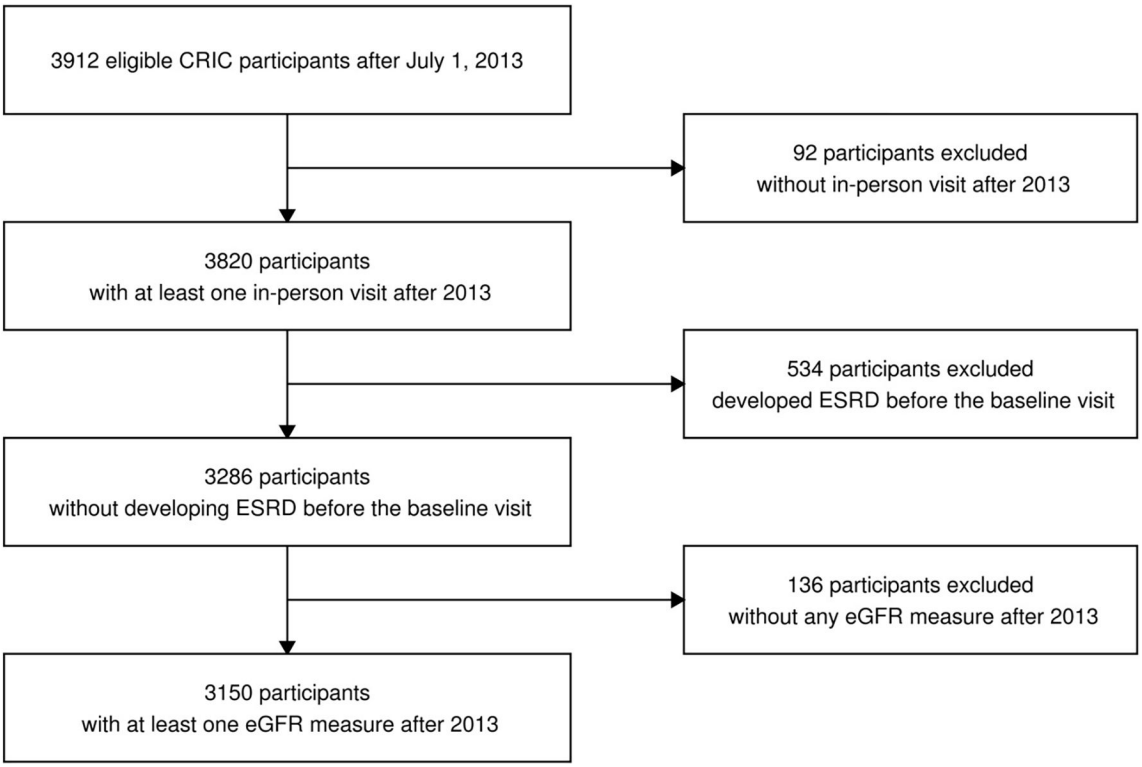

Figure 1:

Participant flow diagram - CRIC: Chronic Renal Insufficiency Cohort study; eGFR estimated glomerular filtration rate; ESRD: End Stage Renal Disease

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Table 1:

Baseline characteristics of 3,150 CRIC study participants overall and by AKI status during follow-up

Characteristic	No AKI n=2717	AKI n=433	Overall n=3150
Age, years	65 (9)	66 (9)	65 (9)
Female	1174 (43)	202 (47)	1376 (44)
Race/ethnicity			
Non-Hispanic Black	1152 (42)	202 (47)	1354 (43)
Non-Hispanic White	1246 (46)	179 (41)	1425 (45)
Hispanic	228 (8)	43 (10)	271 (9)
Other	91 (3)	9 (2)	100 (3)
Diabetes Mellitus	1396 (51)	291 (67)	1687 (54)
Heart Failure	253 (9)	85 (20)	338 (11)
ACEi or ARBs use	1729 (64)	307 (72)	2036 (65)
uPCR, g/g ¶	0.13 (0.06 – 0.44)	0.17 (0.08 – 0.73)	0.13 (0.06 – 0.47)
eGFRcr, mL/min/1.73m^2	52 (17)	49 (16)	52 (17)
eGFRcys, mL/min/1.73m^2	52 (21)	45 (19)	51 (21)
eGFRcr slope prior to hospitalization, mL/min/1.73m^2 per yr *	−0.61 (0.87)	−0.79 (1.00)	−0.66 (0.90)
eGFRcys slope prior to hospitalization, mL/min/1.73m^2 per yr †	−1.21 (0.75)	−1.33 (0.77)	−1.24 (0.76)
Systolic Blood Pressure, mmHg	126 (19)	130 (21)	127 (19)
Diastolic Blood Pressure, mmHg	69 (12)	68 (13)	69 (12)
Body Mass Index, kg/m^2	32.1 (7.2)	34.6 (8.4)	32.3 (7.3)
Weight (kg)	92 (22)	94 (25)	92 (22)

Data are expressed either as mean (standard deviation), median (interquartile range), or N (%).

CRIC: Chronic Renal Insufficiency Cohort; AKI: acute kidney injury; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; uPCR: urine protein-creatinine ratio; eGFRcr: estimated glomerular filtration rate by serum creatinine; eGFRcys: estimated glomerular filtration rate by serum cystatin C;

¶196 participants missing baseline uPRC (167 among those who never experienced AKI and 29 among those who experienced AKI during follow-up)

*eGFRcr slope prior to hospitalization not defined for study participants who were never hospitalized. Only 1399 of the 2717 participants who never experienced AKI had pre-hospitalization eGFRcr slope values (1313 participants had not been hospitalized and 5 participants had their first hospitalization before the study baseline)

†eGFRcys slope prior to hospitalization not defined for study participants who were never hospitalized. Only 1397 of the 2717 participants who never experienced AKI had pre-hospitalization eGFRcys slope values (1313 participants had not been hospitalized, 5 participants had their first hospitalization before the study baseline and 2 participants did not have any pre-hospitalization cystatin C value)

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Table 2:

Multivariable mixed effects model showing association of AKI with CKD progression using the 2021 CKI-EPI SCr equation

	Change in eGFRcr value after each AKI, ml/min/1.73 m^2 (95% CI)	Change in eGFRcr slope after each AKI, ml/min/1.73 m^2 per year (95% CI)
Unadjusted	−2.30 (−3.70, −0.86)	0.20 (−0.23, 0.64)
Model 1	−2.32 (−3.75, −0.89)	0.23 (−0.21, 0.66)
Model 2	−1.81 (−3.23, −0.38)	0.33 (−0.10, 0.76)
Model 3	−1.23 (−2.75, 0.28)	0.22 (−0.24, 0.67)
Model 4	−0.38 (−1.35, 0.59)	0.04 (−0.30, 0.38)

Model 1: adjusted for clinical center and demographic characteristics (age, sex, and race/ethnicity).

Model 2: additionally adjusted for time-updated diabetes, heart failure, systolic blood pressure, receipt of receipt of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs).

Model 3: additionally adjusted for (log transformed) urine protein-creatinine ratio (uPCR).

Model 4: additionally adjusted for baseline estimated glomerular filtration rate (eGFR).

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Table 3:

Multivariable mixed effects model showing association of AKI with CKD progression using the 2012 CKI-EPI cystatin C equation

	Change in eGFRcys value after each AKI, ml/min/1.73 m^2 (95% CI)	Change in eGFRcys slope after each AKI, ml/min/1.73 m^2 per year (95% CI)
Unadjusted	−3.61 (−6.39, −0.82)	0.26 (−0.58, 1.09)
Model 1	−3.53 (−6.28, −0.78)	0.29 (−0.54, 1.12)
Model 2	−2.99 (−5.77, −0.22)	0.31 (−0.53, 1.14)
Model 3	−2.44 (−5.37, 0.49)	0.16 (−0.75, 1.06)
Model 4	−0.15 (−2.16, 1.86)	−0.56 (−1.28, 0.17)

Model 1: adjusted for clinical center and demographic characteristics (age, sex, and race/ethnicity).

Model 2: additionally adjusted for time-updated diabetes, heart failure, systolic blood pressure, receipt of receipt of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs).

Model 3: additionally adjusted for (log transformed) urine protein-creatinine ratio (uPCR).

Model 4: additionally adjusted for baseline estimated glomerular filtration rate (eGFR).