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ORIGINAL ARTICLE

Research-based versus clinical serum creatinine measurements and the association of acute kidney injury with subsequent kidney function: findings from the Chronic Renal Insufficiency Cohort study

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ABSTRACT

Background. Observational studies relying on clinically obtained data have shown that acute kidney injury (AKI) is linked to accelerated chronic kidney disease (CKD) progression. However, prior reports lacked uniform collection of important

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confounders such as proteinuria and pre-AKI kidney function trajectory, and may be susceptible to ascertainment bias, as patients may be more likely to undergo kidney function testing after AKI.

Methods. We studied 444 adults with CKD who participated in the prospective Chronic Renal Insufficiency Cohort (CRIC) Study and were concurrent members of a large integrated healthcare delivery system. We estimated glomerular filtration rate (eGFR) trajectories using serum creatinine measurements from (i) the CRIC research protocol (yearly) and (ii) routine clinical care. We used linear mixed effects models to evaluate the associations of AKI with acute absolute change in eGFR and post-AKI eGFR slope, and explored whether these varied by source of creatinine results. Models were adjusted for demographic characteristics, diabetes status and albuminuria.

Results. During median follow-up of 8.5 years, mean rate of eGFR loss was −0.31 mL/min/1.73 m^2/year overall, and 73 individuals experienced AKI (55% Stage 1). A significant interaction existed between AKI and source of serum creatinine for acute absolute change in eGFR level after discharge; in contrast, AKI was independently associated with a faster rate of eGFR decline (mean additional loss of −0.67 mL/min/1.73 m^2/year), which was not impacted by source of serum creatinine.

Conclusions. AKI is independently associated with subsequent steeper eGFR decline regardless of the serum creatinine source used, but the strength of association is smaller than observed in prior studies after taking into account key confounders such as pre-AKI eGFR slope and albuminuria.

Keywords: acute kidney injury, chronic kidney disease, epidemiology, risk factor

INTRODUCTION

Acute kidney injury (AKI) is an important public health issue that affects up to one in five hospitalizations in the USA [1–6]. While historically an episode of AKI has often been considered a self-limited process followed by recovery of kidney function among survivors, this notion has been challenged by an increasing number of studies demonstrating the interconnected, bidirectional relationship between AKI and chronic kidney disease (CKD) [7–12]. In recent years, observational studies have reported that AKI is closely associated with higher risk of subsequent decline in kidney function, including development of incident CKD and accelerated progression of pre-existing CKD [7–15].

Nevertheless, questions have arisen about the validity of these associations due to the fact that almost all previous observational studies have relied on the use of clinical databases [16, 17]. A potential source of biased estimates from prior studies may be residual confounding by important, but uncaptured shared risk factors for AKI and CKD progression. Particularly important may be degree of proteinuria and rate of kidney function decline before an AKI episode. Few published studies on the impact of AKI on subsequent kidney function trajectory have accounted for potential confounding by proteinuria and preceding estimated glomerular filtration rate (eGFR) slope. Proteinuria may be a particularly important confounder since it has been shown to be a strong risk factor both for development of AKI [8, 18] and for more rapid loss of kidney function [19, 20]. Some have also hypothesized that any more rapid loss of eGFR observed after an episode of AKI mostly reflects more rapid loss of eGFR already present before AKI [21]. Ascertainment bias may also overestimate the strength of association between AKI and subsequent kidney function decline, as patients who survived AKI may get more frequent laboratory monitoring [16, 21].

We addressed these challenges by examining a group of adults with CKD who were both participants in the prospective Chronic Renal Insufficiency Cohort (CRIC) Study [22, 23] and concurrent members of an integrated healthcare delivery system with comprehensive electronic health records. The CRIC Study provided us with protocol-driven kidney function measurements and uniform ascertainment of key confounders such as proteinuria and eGFR slope before AKI, while data from the integrated healthcare delivery system allowed for comprehensive capture of AKI episodes. Pairing of research protocol-driven serum creatinine (SCr) measurements with clinical SCr measurements in the same patients gave us a unique opportunity to explore if any observed associations of AKI with subsequent trajectories of kidney function decline varied by the source of kidney function measurements.

MATERIALS AND METHODS

Study population

We identified the subset of 444 CRIC participants who were concurrent members of Kaiser Permanente Northern California. The CRIC Study is a prospective, multi-center observational cohort study that initially enrolled 3939 adult participants with CKD between 2003 and 2008. The study design, methods and baseline characteristics of CRIC participants have been previously published [22–24]. Adults aged 21–74 years who had an eGFR between 20 and 70 mL/min/1.73 m^2 were recruited from seven clinical centers (13 recruitment sites) in the US. CRIC participants had baseline and annual SCr measurements that were calibrated to isotope dilution mass spectrometry-traceable standards within a central research laboratory at the University of Pennsylvania.

Kaiser Permanente Northern California is a large integrated healthcare delivery system currently caring for >4.3 million members throughout the San Francisco and greater Bay area. Essentially all care provided is captured through a comprehensive electronic health record system, including hospitalizations and laboratory data from ambulatory/inpatient settings. Less than 10% of hospitalizations for Kaiser Permanente members occur outside of Kaiser Permanente hospitals and even in those cases, for financial reasons, patients are frequently repatriated back to Kaiser Permanente-owned facilities to complete inpatient stays, so the extent of missing data is small.

The parent CRIC Study and this ancillary study were approved by the institutional review boards of Kaiser Permanente Northern California and the University of California, San Francisco.

Identification of AKI

The primary predictor was the occurrence of AKI detected within a Kaiser Permanente Northern California hospital from

enrollment in CRIC through 13 January 2015. We defined AKI as a ≥50% relative increase from the nadir to peak inpatient SCr concentration within a hospitalization during our study period. This more stringent definition was adapted from contemporary consensus AKI definitions [25, 26] to increase the likelihood of a true AKI episode, as the inclusion of small absolute changes in SCr (i.e. by 0.3 mg/dL only) may misclassify patients, especially at higher baseline SCr values [27]. The peak inpatient SCr may follow or precede the nadir inpatient creatinine as we were interested in capturing both community-acquired and hospital-associated/hospital-acquired cases of AKI. We deliberately chose not to use outpatient SCr as baseline to determine whether AKI occurred in order to avoid using outpatient SCr to define both the exposure and the outcome, which may lead to undesirable coupling in the analysis. Instead, we felt it was cleaner to define the exposure—AKI—using only inpatient SCr values, and define the outcome—outpatient eGFR trajectory—using only outpatient SCr values. Urine output criteria were not incorporated due to lack of systematically available data [28]. Severity of AKI was based on relative change in SCr in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) stages [25] (with all dialysis-treated AKI categorized as Stage 3). We used the first episode of inpatient AKI observed during the study period for any participant.

Period of observation and measurements of outcome

Participants were followed from the date of CRIC enrollment until death, development of ESRD (defined as receipt of maintenance dialysis or kidney transplant) or the date of last available CRIC research SCr measurement through 13 January 2015 or end of health plan membership. The main outcome of interest was trajectory of kidney function modeled using outpatient eGFR values before and after an episode of AKI. We calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [29] on the basis of age, sex, race and SCr. Two sources of outpatient SCr data were available for each patient to calculate eGFR: (i) measurements performed annually as part of the CRIC research protocol and (ii) measurements performed in the outpatient, non-emergency department setting as part of routine clinical care at Kaiser Permanente Northern California.

Again, inpatient measurements of SCr from Kaiser Permanente Northern California were only used to ascertain AKI status (primary exposure) but not for the outcome of interest (trajectory of outpatient kidney function). SCr measurements in Kaiser Permanente Northern California have also been calibrated to isotope-dilution mass spectrometry-traceable standards [30, 31].

Covariates

Age, sex, self-reported race, diabetes status and degree of albuminuria were defined using baseline CRIC visit data [22–24]. For this analysis, race categories were black versus nonblack. Diabetes was defined as self-reported use of diabetes medications or having a fasting glucose ≥126 mg/dL or nonfasting glucose ≥200 mg/dL [23, 32]. Four categories of albuminuria were defined using urine albumin-to-creatinine ratios (ACR) obtained at entry to CRIC: ACR <30 mg/g (reference); 30 mg/g ≤ ACR ≤ 299 mg/g; 300 mg/g ≤ ACR ≤ 999 mg/g; and ACR ≥1000 mg/g [22, 23].

Statistical analysis

We used linear mixed effects models to determine the association between an episode of AKI and (i) subsequent absolute change in outpatient eGFR and (ii) subsequent rate of eGFR decline (i.e. change in eGFR slope). Both clinical and research outpatient eGFRs were entered in the model, with the primary predictor being time-updated AKI. Covariates in the model include: age, sex, race, baseline albuminuria category, diabetes status, source of SCr (clinical versus research), an interaction term for AKI and source of SCr, time since enrollment in CRIC (to describe the eGFR decline over time) and time elapsed since AKI among those with an AKI episode during the study period (to describe the change in eGFR decline over time after an AKI episode). This model estimates the rate of eGFR as a linear function over time, taking into account the varying number and spacing of measurements of eGFR from the two sources (clinical versus research) as well as the variable follow-up time for each subject. A major advantage of using mixed effects modeling is that it takes into account all of the outpatient eGFR readings for a given person (versus a strategy of only comparing a single pre-hospitalization eGFR used as the referent to a single post-hospitalization eGFR). This approach also reduced the effect of noise due to random measurement error in any given outpatient eGFR reading and handles well variations in number of eGFR readings and spacing between them. We hypothesized that an episode of AKI would be associated with both an absolute decrease in outpatient eGFR level as well as a subsequently steeper (i.e. more negative) slope in eGFR.

We next explored whether the strengths of these associations may vary depending on the source of SCr used to calculate eGFR. Testing the interaction between source of SCr and AKI allowed us to determine if the absolute change in the next available outpatient eGFR measurement post-AKI differed according to the source of SCr measurement. Testing the interaction between source of SCr and time elapsed after AKI allowed us to determine if eGFR trajectory (i.e. slope) differed according to the source of SCr measurement. Supplementary data, Figure S1 conceptualizes the linear mixed effects model with the interactions tested. Analyses were performed using SAS, v9.3 (Cary, NC, USA).

RESULTS

Among 444 eligible patients, mean age at CRIC enrollment was 60.3 years; 67% were women; 34% were black; and mean baseline eGFR was 51.0 mL/min/1.73 m^2 (Table 1). Nearly 40% of patients had a baseline urine ACR ≥30 mg/g, and >30% had diabetes at study entry. Median observation period was 8.5 years [interquartile range (IQR) 4.5–9.8 years]. Seventy-three participants (16% of cohort) experienced at least one episode of AKI, with 45% being Stage 2 or worse (Table 1). Among AKI patients, the median time to AKI was 3.6 years (IQR 1.6–5.5 year). Among these 73 participants, most of them (>80%) had only one episode of AKI episode during the study period. The median post-AKI observation period among the 73 participants who experienced AKI was 2.3 (IQR 0.6–6.0) years.

During the observation period, participants received more clinical SCr measurements than research Cr measurements (median 14 clinical versus 8 research; $P < 0.001$). Among the 73 patients who experienced an episode of AKI, there were also significantly more clinical SCr measurements (median 10 measurements) than research SCr measurements (median 4 measurements) after each patient's AKI episode (Table 2).

Table 1. Characteristics of study participants at baseline and during period of study observation through 13 January 2015

Baseline characteristics	$n = 444$
Age, mean (SD), years	60.3 (9.0)
Women, *n* (%)	297 (66.9)
Black race, *n* (%)	150 (33.8)
eGFR, mean (SD), mL/min/1.73 m^2	51.0 (15.2)
Urine ACR, *n* (%)	
<30 mg/g	269 (60.6)
≥30 mg/g to ≤299 mg/g	91 (20.5)
≥300 mg/g to ≤999 mg/g	42 (9.5)
≥1000 mg/g	42 (9.5)
Diabetes mellitus, *n* (%)	141 (31.8)
Characteristics during period of study observation	
Duration of observation, years	
Mean (SD)	7.1 (3.3)
Median (IQR)	8.5 (4.4–9.8)
Developed AKI during period of observation, *n* (%)	73 (16.0)
Stage 1, *n* (% of all AKI)	40 (54.8)
Stage 2, *n* (% of all AKI)	17 (23.3)
Stage 3 without dialysis, *n* (% of all AKI)	12 (16.4)
Stage 3 with dialysis, *n* (% of all AKI)	4 (5.5)

SD, standard deviation.

Absolute change in outpatient eGFR after AKI

Applying linear mixed effects regression using aggregated data from both sources of SCr measurements to calculate eGFR values, we observed a small apparent absolute rise in mean outpatient eGFR level by 2.01 mL/min/1.73 m^2 after AKI (Table 3). There was a statistically significant interaction ($P = 0.003$) between an episode of AKI and source of SCr with subsequent acute change in mean outpatient eGFR. In models stratified by the source of SCr, we observed a small acute rise in mean eGFR level after AKI when only using clinically obtained SCr (2.20 mL/min/1.73 m^2; $P < 0.0001$) and a small decrease in mean eGFR level after AKI when using only research SCr data that were not statistically significant (−0.35 mL/min/1.73 m^2; $P = 0.69$; Table 3).

Change in eGFR slope after AKI

Applying linear mixed effects regression using aggregated data from both sources of SCr measurements, we found the mean slope of eGFR to be −0.31 mL/min/1.73 m^2/year, reflecting a referent group of patients with mean age 60.3 years, non-black race, male sex, with ACR <30 mg/g, without diabetes and without having experienced AKI. In other words, this slope reflects the pre-AKI slope for 73 participants who experienced AKI and the overall slope for the remainder of the cohort who did not experience AKI. An episode of AKI was associated with an incrementally faster rate of eGFR decline with an additional faster rate of decline by −0.67 mL/min/1.73 m^2/year ($P < 0.0001$; Table 3). In other words, the mean post-AKI slope was $-0.31 + (-0.67) = -0.98$ mL/min/1.73 m^2/year. There was no statistically significant interaction between time elapsed after AKI and source of SCr.

DISCUSSION

In this longitudinal analysis of a unique prospective cohort of adults with CKD who had repeated SCr measurements, we found that an episode of AKI was independently associated with a faster rate of subsequent kidney function decline—by a mean additional loss of −0.67 mL/min/1.73 m^2/year. This degree of change in eGFR slope is quite modest compared with effect sizes reported in previous observational studies addressing changes in kidney function trajectory after AKI. At the same time, we found that the source of SCr may impact the observed association of AKI with subsequent absolute change in the next measured outpatient eGFR level, as clinical data were associated with a paradoxical small rise in the level of the next observed outpatient eGFR, while research protocol-driven data were associated with no significant change.

Animal models of AKI have shed light on potential mechanisms of maladaptive repair after AKI, characterized by fibrosis, vascular rarefaction, tubular loss, glomerulosclerosis and chronic interstitial inflammation—resulting in a state that mimics accelerated kidney aging and functional decline [33–36]. Therefore, even modestly steeper eGFR slope after AKI may represent significant manifestations of accelerated CKD. However, controversy exists about whether AKI causes or worsens CKD, owing to the observational nature of prior human studies and inherent limitations such as the lack of protocol-driven kidney function assessments before and after AKI in clinical practice and the lack of uniform ascertainment of key confounders [16, 17, 37].

Our study builds upon the existing body of literature studying AKI as a risk factor for CKD progression, but incorporates significant methodological strengths to address shortcomings of prior studies. Importantly, we were able to account for important potential confounders in the relationship between AKI and CKD progression that previous studies were not able to fully capture, thanks to CRIC's uniform collection of a complete set of established risk factors such as preexisting albuminuria, diabetes, lower baseline eGFR and steeper eGFR trajectory prior to AKI. As noted above, few studies have simultaneously attempted to control rigorously for pre-AKI proteinuria and pre-AKI eGFR slope, two key potential confounders often neglected in prior studies reporting that patients who experienced AKI had more rapid decline in eGFR than their counterparts who did not [21]. Our adjustment for these key variables may help to explain the more modest, independent effect size in the change in eGFR slope after AKI that we noted, in contrast to prior studies. For example, in a study analyzing data from US Veterans, Amdur *et al.* found that an episode of AKI was associated with a relative drop in eGFR by >10% both in the immediate 1–3 month period and the subsequent 3–12 month period after AKI, equivalent to an additional loss of eGFR by as much as approximately −10 mL/min/1.73 m^2/year [13]. These estimates without adjusting for albuminuria and slope of eGFR before AKI may overestimate the independent effect of AKI on subsequent kidney function decline. In a separate study, James *et al.* used provincial data from Alberta to study patients undergoing coronary angiography and found that patients who had post-angiography AKI had a steeper eGFR slope (from −0.8 mL/min/1.73 m^2/year after mild AKI to −2.8 mL/min/1.73 m^2/year after more severe AKI) compared with those without AKI after angiography (−0.1 mL/min/1.73 m^2/year) [38]. While the authors of that study modeled eGFR trajectory in a similar fashion to our current analysis and attempted to account for proteinuria and baseline rates of kidney function, there was considerable missing data on both proteinuria (~22%) and pre-angiography eGFR decline (~40%) [38].

In addition, we uniquely addressed the important methodological question of potential ascertainment bias in previous reports. As nearly all prior studies [9–12, 38–40] have not used

Table 2. Frequency of serum creatinine testing based on research protocol versus clinical measurements, overall and in the subset of participants experiencing AKI

Testing during period of observation	Research protocol obtained measurements	Clinically obtained measurements	P-value
Number of eGFRs observed among entire cohort ($n = 444$)			
Mean (SD)	7 (3)	16 (14)	<0.0001
Median (IQR)	8 (4–10)	14 (8–22)	<0.0001
Number of eGFRs pre-AKI among entire cohort[a] ($n = 444$)			
Mean (SD)	6 (4)	14(12)	<0.0001
Median (IQR)	7 (3–10)	12 (6–18)	<0.0001
Number of eGFRs pre-AKI among those experiencing AKI ($n = 73$)			
Mean (SD)	4 (2)	9 (8)	<0.0001
Median (IQR)	3 (2–6)	8 (3–13)	<0.0001
Number of eGFRs post-AKI among those experiencing AKI ($n = 73$)			
Mean (SD)	4(3)	16 (19)	<0.0001
Median (IQR)	4 (2–6)	10 (5–20)	<0.0001
Days between AKI discharge date and first post-AKI eGFR ($n = 73$)			
Mean (SD)	128 (70)	107 (286)	0.66
Median (IQR)	119 (68–185)	10 (5–58)	0.01

[a]Includes participants who did not experience AKI during observation.
SD, standard deviation.

Table 3. Multivariable mixed effects model showing association of AKI and other predictors on kidney function

Predictors in the model	Coefficient (95% CI)
Impact of an AKI episode on acute change in level of eGFR[a], ml/min/1.73 m^2	2.01 (1.17–2.84)
Impact of an AKI episode on acute change in level of eGFR using only clinical serum creatinine measurements, ml/min/1.73 m^2	2.20 (1.26–3.13)
Impact of an AKI episode on acute change in level of eGFR using only research serum creatinine measurements, ml/min/1.73 m^2	−0.35 (−2.10 to 1.40)
Impact of an AKI episode on subsequent rate of eGFR decline[b], ml/min/1.73 m^2/year	−0.67 (−0.88 to −0.46)

[a]Test of interaction between AKI and source of serum creatinine P = 0.003.
[b]Test of interaction between time elapsed after AKI and source of serum creatinine P = 0.06.

prospectively collected data but instead relied solely on SCr measurements obtained as a part of routine clinical care, they were susceptible to bias of more frequent surveillance of kidney function among patients with AKI [16, 21]. In the present study, although we observed that patients who had AKI had significantly more frequent SCr measurements obtained as a part of routine clinical care, we found a similar magnitude in rate of additional eGFR loss after AKI with no significant interaction with source of SCr.

In modeling the association of an AKI episode and acute absolute change in outpatient eGFR, we interestingly found a statistically significant interaction between AKI and source of SCr, with observed absolute differences that were small but in opposite directions when using only clinical versus only research SCr measurements (Table 3). This finding may reflect that the majority of AKI cases in our cohort were mild (55% Stage 1) and that kidney function may recover back to a baseline eGFR level by the time the next outpatient measurement is obtained. This is in contrast to the aforementioned study by Amdur *et al.*, in which >50% of the cases of AKI defined using administrative codes met criteria for severe (Stage 3) AKI, and which showed an crude acute drop in eGFR by 10% post-AKI [13]. The paradoxical improvement in eGFR following an episode of AKI using clinical measurements only may be because patients hospitalized with acute illness often develop significant reductions in SCr concentration at or immediately post discharge, as shown in a previous study by Prowle *et al.* [41]. This fall in SCr may be due to hemodilution from volume resuscitation or acute illness-associated loss of muscle mass, which leads to decreased creatinine generation [41, 42]. These factors may be less important further out after a hospitalization when the research SCr measurements tended to be done.

We believe that our observation of the modest impact of an AKI episode on kidney function trajectory after accounting for potential confounders is novel and important. It helps to reconcile the apparent contradiction in the existing literature [16, 17] on the strength and causality of the AKI–CKD link. While many observational studies show an association between AKI and worse kidney function in the subsequent months to years [15], the few analyses of randomized controlled trials in which the interventions modestly affected rates of AKI showed no apparent impact on long-term observed kidney function [37, 43]. In the Coronary Artery Bypass Grafting Surgery Off- or On-pump Revascularization kidney function sub-study that randomized 2932 patients to 'off-pump' versus 'on-pump' surgery, Garg *et al.* observed that, despite a modest reduction in post-operative AKI incidence in the group randomized to off-pump surgery, there was no statistically significant difference in kidney function at 1 year [37]. In that study, however, only 19% of participants experienced AKI, and >60% of the AKI cases were mild in severity (i.e. <100% increase in SCr) [37]. Therefore, the observed eGFR results at 1 year after intervention was determined largely by individuals who did not experience AKI (81%) plus individuals who experienced mild AKI (11%). It is likely that the

combination of only a minority of patients in randomized trials experiencing AKI, interventions that only modestly changed AKI rates and the impact of AKI that was mild in severity on subsequent eGFR being modest (as quantified by our current study)—helps to reconcile this controversy in the literature.

Our findings may have important practice implications. For example, providers should be cautious in assigning new baseline eGFR after an AKI episode, as data from our study and others [41] suggest the potential for falsely normal or elevated eGFR in the early post-hospitalization period after AKI when relying on clinical SCr measurements. Healthy People 2020 lists as one of its goals to increase the proportion of AKI survivors who have follow-up renal function evaluation within 6 months post-discharge [44], a practice also promoted by the 2012 KDIGO Clinical Practice Guidelines for AKI [25] and the AKI Advisory Group of the American Society of Nephrology [45]. If the impact of mild AKI on subsequent kidney function decline is quite modest, it would seem prudent to prioritize early nephrology involvement during the post-AKI course for higher risk individuals, such as those with preexisting CKD and those who survived more severe forms of AKI [46] rather than instituting blanket post-AKI care components for everyone.

Our study has some limitations. Our approach may exclude some patients with community-acquired AKI, who are admitted with SCr values that were higher than their steady state preadmission baseline value and who do not recover sufficiently during hospitalizations to meet the [peak/nadir SCr] ratio threshold we used to define AKI. However, in those cases, it may be difficult to distinguish whether a person truly had AKI or just relatively rapid progression of underlying CKD since both those scenarios can give the observed SCr patterns. Validated urine output data were not available [28]. We also lacked more granular data from hospitalizations to characterize potential causes of AKI, as different etiologies (e.g. acute tubular necrosis vs prerenal azotemia) may produce different estimates on the impact of AKI on CKD progression. Our sample size was not large. However, our confidence intervals indicate that we estimated effect sizes with reasonable precision. The predominantly milder AKI episodes and modest absolute number of AKI episode meant that our results cannot be fully extrapolated to severe AKI (e.g. dialysis-requiring AKI) in which the data are much stronger that it substantially accelerates kidney function loss [9, 10]. The time gap between episodes of AKI and measurement of outpatient eGFR (both before and after) was not controlled but this should not introduce substantial biases as the mixed effect models takes into account information from all study participants (both those with and those without AKI) to model individual (as well as group level) eGFR trajectories and can handle well variations in spacing of eGFR readings. The model does assume that kidney function uniformly declines in a linear fashion over time [47, 48]. Within the time frame of our study and frequency of outpatient eGFR measurements, this is not an unreasonable assumption [49, 50] and one would expect any deviation to affect both those who did and did not experience AKI.

In conclusion, AKI appears to be independently associated with accelerated subsequent kidney function decline, but the adjusted effect size was much smaller than previously reported after accounting for potential confounders, including pre-AKI proteinuria and eGFR slope. The source of SCr measurements before and after an episode of AKI used to estimate kidney function may influence the observed association with AKI depending on the outcome studied. Larger studies using longitudinal data from protocol-driven, more frequent measurements of SCr, or from alternative filtration markers that may be less impacted by acute illness such as serum cystatin C [51], are needed to clarify the link between AKI and subsequent kidney function loss. In addition, uniform ascertainment and adjustment for pre-AKI factors such as proteinuria and eGFR slope are paramount toward minimizing residual confounding in elucidating this association.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

R.K.H., C.-y.H., C.E.M., J.Y. and A.S.G. were involved in research idea and study design; R.K.H., C.-y.H., C.E.M., J.Y., A.H.A., J.C., H.I.F., J.H., S.D.N., M.R., T.C.T., D.X., X.Z. and A.S.G. were involved in data acquisition and analysis; all authors interpreted the data; C.-y.H., C.E.M. and A.S.G. supervised; R.K.H., C.-y.H., J.Y., T.C.T. and A.S.G. contributed to manuscript drafting; all authors were involved in revision of manuscript. All authors were responsible for providing intellectual content of critical importance to the work described as well as for final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously except in abstract form. The authors declare no relevant conflicts of interest.

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