JAMA Internal Medicine | Original Investigation

Post–Acute Kidney Injury Proteinuria and Subsequent Kidney Disease Progression

The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study

Chi-yuan Hsu, MD, MSc; Vernon M. Chinchilli, PhD; Steven Coca, DO, MS; Prasad Devarajan, MD; Nasrollah Ghahramani, MD; Alan S. Go, MD; Raymond K. Hsu, MD, MAS; T. Alp Ikizler, MD; James Kaufman, MD; Kathleen D. Liu, MD, PhD; Chirag R. Parikh, MD, PhD; W. Brian Reeves, MD; Mark Wurfel, MD, PhD; Michael Zappitelli, MD, MSc; Paul L. Kimmel, MD; Edward D. Siew, MD, MSCI; for the ASSESS-AKI Investigators

IMPORTANCE Among patients who had acute kidney injury (AKI) during hospitalization, there is a need to improve risk prediction such that those at highest risk for subsequent loss of kidney function are identified for appropriate follow-up.

OBJECTIVE To evaluate the association of post-AKI proteinuria with increased risk of future loss of renal function.

DESIGN, SETTING, AND PARTICIPANTS The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study was a multicenter prospective cohort study including 4 clinical centers in North America included 1538 patients enrolled 3 months after hospital discharge between December 2009 and February 2015.

EXPOSURES Urine albumin-to-creatinine ratio (ACR) quantified 3 months after hospital discharge.

MAIN OUTCOMES AND MEASURES Kidney disease progression defined as halving of estimated glomerular filtration rate (eGFR) or end-stage renal disease.

RESULTS Of the 1538 participants, 769 (50%) had AKI durring hospitalization. The baseline study visit took place at a mean (SD) 91 (23) days after discharge. The mean (SD) age was 65 (13) years; the median eGFR was 68 mL/min/1.73 m^2; and the median urine ACR was 15 mg/g. Overall, 547 (37%) study participants were women and 195 (13%) were black. After a median follow-up of 4.7 years, 138 (9%) participants had kidney disease progression. Higher post-AKI urine ACR level was associated with increased risk of kidney disease progression (hazard ratio [HR], 1.53 for each doubling; 95% CI, 1.45-1.62), and urine ACR measurement was a strong discriminator for future kidney disease progression (C statistic, 0.82). The performance of urine ACR was stronger in patients who had had AKI than in those who had not (C statistic, 0.70). A comprehensive model of clinical risk factors (eGFR, blood pressure, and demographics) including ACR provided better discrimination for predicting kidney disease progression after hospital discharge among those who had had AKI (C statistic, 0.85) vs those who had not (C statistic, 0.76). In the entire matched cohort, after taking into account urine ACR, eGFR, demographics, and traditional chronic kidney risk factors determined 3 months after discharge, AKI (HR, 1.46; 95% CI, 0.51-4.13 for AKI vs non-AKI) or severity of AKI (HR, 1.54; 95% CI, 0.50-4.72 for AKI stage 1 vs non-AKI; HR, 0.56; 95% CI, 0.07-4.84 for AKI stage 2 vs non-AKI; HR, 2.24; 95% CI, 0.33-15.29 for AKI stage 3 vs non-AKI) was not independently associated with more rapid kidney disease progression.

CONCLUSIONS AND RELEVANCE Proteinuria level is a valuable risk-stratification tool in the post-AKI period. These results suggest there should be more widespread and routine quantification of proteinuria after hospitalized AKI.

JAMA Intern Med. doi:10.1001/jamainternmed.2019.6390
Published online January 27, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The ASSESS-AKI Investigators appear at the end of the article.

Corresponding Author: Chi-yuan Hsu, MD, MSc, Division of Nephrology, University of California, San Francisco, 533 Parnassus Ave, U-400, PO Box 0532, San Francisco, CA 94143 (hsuchi@medicine.ucsf.edu).

An episode of acute kidney injury (AKI) is strongly associated with more rapid subsequent loss of kidney function.[1,2] There is a need to improve risk prediction so that those at highest risk for kidney disease progression are identified for appropriate follow-up.[3-10]

Several recent publications have stressed the prognostic importance of post-AKI level of serum creatinine (SCr) or estimated glomerular filtration function (eGFR).[11-13] For example, Stoumpos et al[11] reported that even among patients who had severe AKI requiring dialysis, those who had a post-AKI eGFR level greater than 60 mL/min/1.73 m^2 had low risk of accelerated loss of kidney function, leading these authors to suggest that special monitoring is not necessary.

Two new studies[14,15] report that proteinuria level increases after an episode of AKI, potentially reflecting residual renal parenchymal injury. We hypothesize that the level of proteinuria after AKI is strongly associated with subsequent loss of kidney function,[16-18] although this was not seen in a small prospective study.[19] We further hypothesize that known risk factors for future loss of kidney function that are readily available—namely proteinuria, eGFR level, and demographics—can very successfully risk stratify patients after AKI as they do in other at-risk populations.[16-18] Indeed, it is possible that once post-AKI proteinuria, post-AKI eGFR, and other known chronic kidney disease (CKD) risk factors are taken into account, patients who had AKI during hospitalization have similar renal prognosis—and thus do not need to be triaged differently—compared with hospitalized patients who did not have AKI.

To test these hypotheses, we analyzed data from a multicenter cohort study of patients enrolled 3 months after hospital discharge—half of whom had an episode of AKI while hospitalized.

Key Points

Question Among patients who had acute kidney injury (AKI) during hospitalization, is proteinuria quantified after hospital discharge associated with future loss of renal function?

Findings In this matched cohort study of 1538 participants, half of whom had AKI during hospitalization, higher urine albumin-to-creatinine ratio quantified 3 months after discharge from a hospitalization with AKI was associated with increased risk of kidney disease progression and served as a risk discriminator.

Meaning More widespread quantification of proteinuria after hospitalized AKI should be considered to better evaluate the risk of future kidney disease progression.

Methods

Study Population

The Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study was a prospective, matched cohort study of 1538 hospitalized adults who did or did not have an episode of AKI and survived to complete a study visit 3 months after discharge (eFigure in the Supplement).[20] Patients enrolled between December 2009 and February 2015 from 4 North American clinical centers involving various hospital settings (general medical and surgical wards, intensive care units [ICU], and postcardiac surgery). The study was approved by institutional review boards of the participating institutions, and written informed consent was obtained from participants.

For the 769 hospitalized adults (age ≥18 years) who experienced an episode of AKI, AKI was defined based on a relative increase of at least 50% or 0.3 mg/dL or more in inpatient SCr concentration above the nearest outpatient, non-emergency department SCr concentration obtained 7 to 365 days prior to index hospitalization.[20] We concurrently enrolled a matched sample of 769 adults without AKI at the index hospitalization. Patients were initially matched on clinical center and preadmission chronic kidney disease (CKD) status (eGFR<60 mL/min/1.73 m^2), with additional matching on an integrated priority score based on age, history of cardiovascular disease, diabetes mellitus status, category of preindex hospitalization eGFR,[20,21] and treatment in the ICU. Exclusion criteria included lack of outpatient, non-emergency department SCr reading 7 to 365 days prior to index hospitalization, previously receiving chronic renal replacement therapy or having an eGFR of less than 15 mL/min/1.73 m^2 prior to hospitalization, prior organ or hematopoietic cell transplant, acute glomerulonephritis or clinically significant urinary tract obstruction, hepatorenal syndrome, metastatic or actively treated cancer, multiple myeloma, New York Heart Association class IV heart failure, an index hospitalization lasting 90 days or longer, remaining on dialysis 3 months after index hospitalization discharge, active pregnancy, or predicted survival of 12 months or less.[20]

These 1538 ASSESS-AKI study participants all had an outpatient research study visit 3 months after index hospitalization discharge, during which clinical data and biosamples were systematically collected.[20] This visit was considered the ASSESS-AKI baseline study visit. A follow-up ASSESS-AKI in-person study visit was conducted annually thereafter, with interim telephone contacts at approximately 6-month intervals.[20] Medical history, study events, and use of medications were updated at each in-person or telephone contact, and eGFR requantified at each in-person visit.

Exposures

All participants had random urine albumin-to-creatinine ratio (ACR) quantified at the ASSESS-AKI baseline study visit. Participant SCr concentration was measured concurrently to calculate CKD-EPI equation eGFR.[21] Serum creatinine concentration (and urine creatinine concentration) was measured using the Roche enzymatic method (Roche Diagnostics) on a Roche ModP Chemistry Analyzer before January 2014 and Cobas 6000 Chemistry Analyzer afterwards. The method was calibrated, and checked semiannually, using a National Institute of Standards and Technology (NIST) standard traceable to reference material SRM 909b (Isotope Dilution Mass Spectroscopy [IDMS]). Urine albumin concentration was quantified using a nephelometric method on the Siemens ProSpec analyzer (Siemens GMBH).

Other exposures of interest included presence or absence of AKI and stage of AKI. Participants' AKI was staged based on SCr concentration changes with 2.0 to 2.9 times change indicating stage 2 AKI and 3.0 or more times change (or initiation of acute renal replacement therapy) indicating stage 3 AKI.[22]

Primary Outcome

Our primary outcome was kidney disease progression defined as halving of eGFR or end-stage renal disease (ESRD, defined as receipt of chronic dialysis or kidney transplant).[20,23-29] Halving of eGFR was calculated relative to the eGFR measured at the ASSESS-AKI baseline study visit. Follow-up occurred through November 30, 2018 (eTable 1 in the Supplement).

Statistical Analysis

The ASSESS-AKI DCC started the original analysis in November 2018. The revised analyses was undertaken in September 2019. We conducted time-to-event analysis using Cox proportional hazards models,[30] after confirming there was no violation of the proportional hazards assumption. We accounted for the 1-to-1 matching with a random (frailty) effect. Our primary metric to assess ability of the model to risk discriminate was the C statistic.[31]

We conducted analyses separately in the 769 participants who had AKI during the index hospitalization and the 769 participants who did not and then in all 1538 ASSESS-AKI participants. We built separate unadjusted models with only urine ACR or only AKI (or AKI stages) (or only eGFR) as the predictor as well as adjusted models with urine ACR and AKI (or AKI stages) along with concurrently assessed eGFR, demographics, systolic blood pressure (SBP), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and presence or absence of diabetes mellitus.[16,17,32-34] We also included an interaction term between AKI (or AKI stages) and urine ACR to examine whether urine ACR was associated with kidney disease progression similarly both among those with and without medical history of AKI (and with different severities of AKI).

We then conducted a series of sensitivity analyses, including examining only the subset of AKI participants who had inpatient SCr concentration at least 50% higher than nearest outpatient, non-emergency department SCr concentration obtained 7 to 365 days prior to index hospitalization; requiring that halving of eGFR be confirmed by 2 consecutive values when defining kidney disease progression; additionally adjusting for smoking status and angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) use at the baseline ASSESS-AKI study visit; additionally adjusting for change in eGFR from prehospitalization to posthospitalization (in mL/min/1.73 m^2 per month); and implementing a competing risks regression based on Fine and Gray's proportional subhazards model. We also repeated our entire analysis replacing urine ACR with urine protein-to-creatinine ratio (PCR). Urine total protein was measured using a turbidimetric method (Roche Diagnostics).

Finally, we conducted a secondary analysis examining as exposure the risk of ESRD over 5 years as predicted from the validated Kidney Failure Risk Equation (KFRE),[35] which has been shown to have strong discriminatory power and is well calibrated in general CKD populations.[17,33] The KFRE is calculated using only age, sex, eGFR, urine ACR, and region (North America or not). The outcome in this secondary analysis was limited to ESRD.

Results

The baseline ASSESS-AKI study visit took place a mean (SD) 91 (23) days after index hospital discharge. At that visit, median age of the 1538 matched adult study participants was 66 (interquartile range [IQR], 57-74) years; median eGFR was 68 (IQR, 50-89) mL/min/1.73 m^2, median urine ACR was 15 (IQR, 7-60) mg/g; 574 (37%) were women, 195 (13%) were black, and 660 (43%) had diabetes mellitus. After a median follow-up of 4.7 years, 138 participants had kidney disease progression and there were 58 cases of ESRD observed (eTable 1 in the Supplement).

By design, during the index hospitalization prior to the baseline ASSESS-AKI study visit, 769 participants experienced AKI and 769 did not. Among the former, 118 (15%) were stage 2 in severity and 98 (13%) were stage 3 (including 26 who required renal replacement therapy but then recovered to stop dialysis). Median duration of AKI was 2 (IQR, 1-5) days. As shown in **Table 1**, those who had AKI had on average lower eGFR before and after the index hospitalization.

Among the 769 participants who had AKI during hospitalization, 97 had kidney disease progression (2.9 events per person-years). Higher urine ACR levels 3 months after discharge were associated with higher risk of kidney disease progression (**Figure**) (HR, 1.53 for each doubling; 95% CI, 1.43-1.64). Post-AKI urine ACR was associated with increased risk of kidney disease progression, with a C statistic of 0.82 (**Table 2**). The performance of postdischarge urine ACR was better in patients who experienced AKI than in patients discharged without AKI (C statistic, 0.70) (Table 2). Post-AKI eGFR was also associated with a higher risk of kidney disease progression (HR, 1.50 for each 10 mL/min/1.73 m^2 decrease; 95% CI, 1.36-1.66) but the C statistic for post-AKI urine ACR was higher than that for post-AKI eGFR[11-13] (0.82 vs 0.77; $P < .001$) (Table 2).

A comprehensive model of clinical risk factors (eGFR, blood pressure, and demographics) including ACR provided better discrimination for predicting kidney disease progression after hospital discharge among those who had AKI (C statistic, 0.85) vs those who did not (C statistic, 0.74) (Table 2). Among those who had AKI, adding urine ACR to a model with all the covariates listed in Table 2 (including AKI stages) yielded an increase in C statistics from 0.82 to 0.85 ($P < .001$) (eTable 2 in the Supplement). Net reclassification improvement (NRI)[36] for comparing the model with and without urine ACR was 0.56 ($P < .001$) (eTable 2 in the Supplement).

In the entire ASSESS-AKI matched cohort, after taking into account urine ACR and eGFR, demographics, and traditional CKD risk factors determined 3 months after hospital discharge, neither the presence or absence of AKI nor the sever-

Table 1. Baseline Characteristics of Adult ASSESS-AKI Study Participants With and Without Acute Kidney Injury During Index Hospitalization Prior to Baseline Study Visit

Characteristic	AKI, No. (%)		*P* Value
	With (n = 769)	Without (n = 769)	
Serum creatinine concentration, mean (SD) mg/dL			
Preindex hospitalization	1.24 (0.55)	1.11 (0.44)	<.001
Peak inpatient SCr	2.46 (1.77)	1.11 (0.41)	<.001
ASSESS-AKI baseline study after index hospitalization[a]	1.30 (0.70)	1.07 (0.43)	<.001
Estimated GFR, mean (SD), mL/min/1.73 m^2			
Preadmission	67.2 (25.8)	70.2 (24.1)	<.001
ASSESS-AKI baseline study[a]	65.7 (26.9)	72.7 (24.2)	<.001
Age, mean (SD), y	63.7 (12.8)	65.4 (12.6)	<.001
Women	250 (32.5)	324 (42.1)	<.001
Race			
White	607 (78.9)	653 (84.9)	
Black	117 (15.2)	78 (10.1)	.007
Other	45 (5.9)	38 (4.9)	
Hispanic ethnicity	21 (2.7)	17 (2.2)	.62
Smoking status			
Never	308 (40.0)	326 (42.4)	
Former	344 (44.7)	345 (44.9)	.37
Current	112 (14.6)	90 (11.7)	
Unknown	5 (0.7)	8 (1.0)	
Prior cardiovascular disease	372 (48.4)	321 (41.7)	<.001
Prior diabetes mellitus	387 (50.3)	273 (35.5)	<.001
During admission			
Treated in ICU	545 (70.9)	473 (61.5)	<.001
Vasopressor use	270 (35.1)	215 (28.0)	<.001
Sepsis	118 (15.3)	26 (3.4)	<.001
ASSESS-AKI baseline measurements, mean (SD)[a]			
BMI, mean (SD)[b]	31.6 (8.3)	30.5 (7.0)	.01
Blood pressure, mean (SD), mm Hg			
Systolic	129 (22)	127 (19)	.14
Diastolic	71 (14)	72 (14)	.29
Plasma cystatin C, median (IQR), mg/L	1.21 (0.93-1.59)	1.00 (0.83-1.30)	<.001
Urine PCR, median (IQR), g/g	0.15 (0.08-0.31)	0.12 (0.07-0.22)	<.001
Urine ACR, median (IQR), mg/g	21 (8-118)	11 (6-32)	<.001
30-300, No. (%)	211 (27.4)	149 (19.4)	<.001
>300, No. (%)	119 (15.5)	50 (6.5)	

Abbreviations: ACR, albumin to creatinine ratio; AKI, acute kidney injury; ASSESS-AKI, The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury study; BMI, body mass index; GFR, glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; PCR, protein to creatinine ratio; SCr, serum creatinine.

[a] ASSESS-AKI baseline visit occurred 3 months after index hospitalization.

[b] Calculated as weight in kilograms divided by height in meters squared.

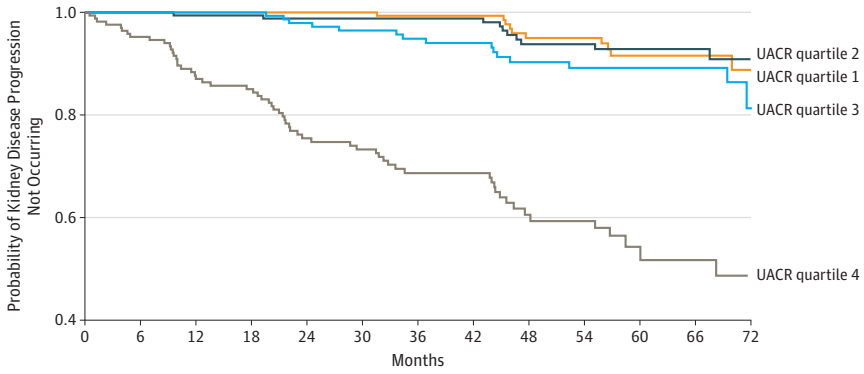
ity of AKI was independently associated with more rapid kidney disease progression (**Table 3**). However, urine ACR remained an independent risk factor after accounting for the other risk factors. There was no interaction between urine ACR and AKI or AKI severity. In other words, urine ACR was associated with kidney disease progression equally both in those with and without a medical history of AKI (and with different AKI severities). The C statistic of the fully adjusted model factoring in AKI severity (0.79) was not higher than that of the model with urine ACR alone (0.80). Estimated glomerular filtration rate remained an independent risk factor for kidney disease progression in all adjusted models (Table 2 and Table 3).

Similar results were seen in all the sensitivity analyses (eTables 3, 4, and 5 in the Supplement). Urine PCR had a stronger association with kidney disease progression than urine ACR (HR, 1.98 vs 1.53 for each doubling). Results of the KFRE secondary analysis are shown in eTable 6 in the Supplement.

Discussion

These findings highlight the prognostic importance of post-AKI proteinuria. The results support 3 hypotheses. First, proteinuria after AKI is associated with subsequent loss of kidney function. As assessed by the C statistic, proteinuria is more significantly associated with subsequent loss of kidney function than post-AKI eGFR level, which has received more attention in the literature.[11-13] Second, the known risk factors for future loss of kidney function which are readily available—including proteinuria and eGFR—can successfully

Figure. Kaplan-Meier Curves Showing Time to Kidney Disease Progression (Defined as Halving of eGFR or ESRD) by Quartiles of Urine ACR (UACR) Among the 769 ASSESS-AKI Enrollees With AKI 3 Months Prior to Baseline ASSESS-AKI Study Visit



No. at risk

UACR quartile 1	192	171	165	165	157	156	141	136	102	96	45	44	15
UACR quartile 2	192	173	166	165	158	156	138	137	100	99	53	48	13
UACR quartile 3	192	171	155	153	136	132	114	111	85	80	47	41	15
UACR quartile 4	192	160	133	128	104	101	82	80	49	45	21	19	6

ACR indicates albumin to creatinine ratio; AKI, acute kidney injury; ASSESS-AKI,the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury Study; eGFR, estimated glomerular filtration function; ESRD, end-stage renal disease

Table 2. Urine ACR, AKI Stage, and Risk of Kidney Disease Progression Among Those With AKI and Those Without AKI

	ASSESS-AKI Enrollees					
	With AKI 3 mo Prior to Baseline Visit (n = 769)			Without AKI 3 mo Prior to Baseline Visit (n = 769)		
Predictors in Model	HR (95% CI)	*P* Value	C Statistic	HR (95% CI)	*P* Value	C Statistic
Unadjusted models						
Higher urine ACR (per doubling), mg/g	1.53 (1.43-1.64)	<.001	0.82	1.45 (1.31-1.61)	<.001	0.70
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.50 (1.36-1.66)	<.001	0.77	1.42 (1.22-1.66)	<.001	0.71
Stage 2 vs stage 1 AKI	0.86 (0.45-1.63)	.64	0.26	NA		
Stage 3 vs stage 1 AKI	1.59 (0.93-2.72)	.09				
Adjusted models						
Higher urine ACR (per doubling), mg/g	1.37 (1.26-1.49)	<.001	0.85	1.24 (1.10-1.40)	.005	0.76
Female vs male	1.43 (0.93-2.22)	.10		1.41 (0.72-2.74)	.32	
Black vs nonblack	0.84 (0.50-1.42)	.51		1.82 (0.82-4.04)	.14	
Hispanic vs non-Hispanic	0.81 (0.25-2.63)	.73		1.64 (0.22-12.32)	.63	
Diabetic vs nondiabetic	1.62 (0.95-2.75)	.08		2.08 (1.06-4.08)	.03	
Older age (per 5 y increase)	0.88 (0.80-0.97)	.01		0.78 (0.67-0.92)	.003	
Higher systolic BP (per 10 mm Hg increase)	1.03 (0.93-1.14)	.54		1.06 (0.91-1.25)	.43	
Higher BMI (per 5 kg/m^2 increase)	0.98 (0.85-1.13)	.79		0.95 (0.79-1.14)	.55	
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.27 (1.15-1.40)	<.001		1.41 (1.20-1.65)	<.001	
Adjusted models (With Stages of AKI)						
Higher urine ACR (per doubling), mg/g	1.38 (1.26-1.50)	<.001	0.85	NA		
Female vs male	1.42 (0.92-2.19)	.12				
Black vs nonblack	0.84 (0.50-1.41)	.50				
Hispanic vs non-Hispanic	0.80 (0.25-2.57)	.70				
Diabetic vs nondiabetic	1.63 (0.96-2.77)	.07				
Older age (per 5 y increase)	0.88 (0.80-0.97)	.01				
Higher systolic BP (per 10 mm Hg increase)	1.03 (0.94-1.14)	.53				
Higher BMI (per 5 kg/m^2 increase)	0.98 (0.85-1.14)	.82				
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.27 (1.16-1.40)	<.001				
Stage 2 vs stage 1 AKI	0.89 (0.46-1.72)	.72				
Stage 3 vs stage 1 AKI	1.96 (1.14-3.37)	.01				

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; ASSESS-AKI, The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury study; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NA, not applicable.

Table 3. Urine ACR, AKI/Stage of AKI and Risk of Kidney Disease Progression Among All ASSESS-AKI Adult Matched Cohort Study Participants (N = 1538)

	All Matched ASSESS-AKI Enrollees (n = 1538)		
Predictors in Model	HR (95% CI)	*P* Value	C Statistic
Unadjusted models			
Higher urine ACR (per doubling), mg/g	1.53 (1.45-1.62)	<.001	0.80
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.55 (1.42-1.70)	<.001	0.76
AKI vs non-AKI	3.06 (2.11-4.44)	<.001	0.39
AKI stage 1 vs no AKI	2.89 (1.94-4.29)	<.001	
AKI stage 2 vs no AKI	2.57 (1.27-5.19)	.009	0.48
AKI stage 3 vs no AKI	4.92 (2.66-9.10)	<.001	
Adjusted model with interaction terms (AKI vs no AKI)			
Higher urine ACR (per doubling), mg/g	1.26 (1.11- 1.43)	<.001	
Female vs male	1.57 (1.00-2.48)	.05	
Black vs nonblack	1.18 (0.68-2.04)	.55	
Hispanic vs non-Hispanic	1.14 (0.32-3.98)	.84	
Diabetic vs nondiabetic	2.27 (1.35-3.83)	.002	
Older age (per 5 y increase)	0.89 (0.80-0.99)	.03	0.79
Higher systolic BP (per 10 mm Hg increase)	1.12 (1.00-1.24)	.04	
Higher BMI (per 5 kg/m^2 increase)	1.02 (0.88-1.18)	.77	
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.17 (1.06-1.30)	.002	
AKI vs no AKI	1.46 (0.51-4.13)	.48	
AKI vs no AKI urine ACR[a]	1.04 (0.90-1.20)	.63	
Adjusted model with interaction terms (stage of AKI vs no AKI)			
Higher urine ACR (per doubling), mg/g	1.25 (1.10-1.43)	<.001	
Female vs male	1.62 (1.02-2.57)	.04	
Black vs nonblack	1.15 (0.66-2.01)	.62	
Hispanic vs non-Hispanic	1.14 (0.32-4.01)	.84	
Diabetic vs nondiabetic	2.31 (1.37-3.91)	.002	
Older age (per 5 y increase)	0.89 (0.80-1.00)	.04	
Higher systolic BP (per 10 mm Hg increase)	1.13 (1.01-1.26)	.03	
Higher BMI (per 5 kg/m^2 increase)	1.02 (0.88-1.18)	.83	0.79
Lower eGFR (per 10 mL/min/1.73 m^2 decrease)	1.18 (1.07-1.31)	.001	
AKI stage 1 vs no AKI	1.54 (0.50-4.72)	.45	
AKI stage 2 vs no AKI	0.56 (0.07-4.84)	.60	
AKI stage 3 vs no AKI	2.24 (0.33-15.29)	.41	
AKI stage 1 vs no AKI urine ACR[a]	1.02 (0.87-1.19)	.80	
AKI stage 2 vs no AKI urine ACR[a]	1.16 (0.88-1.52)	.29	
AKI stage 3 vs no AKI urine ACR[a]	1.07 (0.82-1.40)	.61	

Abbreviations: ACR, albumin-to-creatinine ratio; AKI, acute kidney injury; ASSESS-AKI, The Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury study; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate.

[a] Interaction tests between presence and absence of AKI and amount of urine ACR and between stages of AKI and amount of urine ACR.

risk discriminate patients after AKI as they successfully risk discriminate in other settings.[16-18] Third, once post-AKI proteinuria, post-AKI eGFR, and other known CKD risk factors are taken into account, patients who experience AKI during hospitalization have similar renal prognoses compared with hospitalized patients who did not experience AKI. This is consistent with the recent analysis by James et al,[10] which concluded that discharge SCr was more important than AKI stage. Similarly, in a Canadian study by Sawhney et al,[35] adding AKI to a base risk model already incorporating information regarding post-AKI proteinuria, post-AKI eGFR, and demographics did not improve predictions on comparison of receiver operating characteristics or decision curve analysis.

We prospectively collected data according to a structured research protocol. We were able to quantify post-AKI proteinuria rigorously at a uniform point in time relative to the AKI hospitalization. In contrast, retrospective studies that rely on clinical data collected as part of routine clinical care suffer from ascertainment bias and missing data problems. For example, in a Scottish study by Sawhney et al,[12] post-AKI proteinuria was investigated using a clinical database but fewer than a quarter of participants had this available. Furthermore, timing of assessment was inconsistent and proteinuria could only be dichotomized as normal or abnormal. In their analysis alluded to above, Stoumpos et al[11] did not have data on proteinuria. In the study by James et al,[10] albuminuria values were only semiquantified, were ascertained at varying time points (including before or during the AKI hospitalization) and had a high degree of missingness.

Our findings suggest that there should be more emphasis on testing of proteinuria after AKI. Prior studies of assessment of renal health after AKI have focused almost exclu-

sively on SCr measurements.[37-40] Our results support the Healthy People 2020 objectives (CKD-3) to "Increase the proportion of hospital patients who incurred AKI who have follow-up renal evaluation in 6 months post discharge,"[41] in which renal evaluation is identified by having a microalbuminuria test. In clinical practice, proteinuria is infrequently measured after AKI. For example, in a study[42] of patients with hospitalized AKI from 5 Veterans Affairs hospitals from 2002 to 2009, at 3 months after discharge, proteinuria was quantified on only 6% of patients. According to US Renal Data System data among Medicare patients aged 65 years or older who had AKI during hospitalization in 2015, only 17% had urinary albumin level measured.[41]

Most patients who had AKI of mild to moderate severity will be seen by primary care clinicians, not nephrologists.[3,37] Many of these patients may have hitherto unappreciated renal parenchymal disease predisposing them to AKI or have residual structural damage from the AKI episode,[14,15] placing them at increased risk for future loss of kidney function (and cardiovascular disease).[1,43,44] Our findings demonstrate that proteinuria after AKI carries important prognostic information not conveyed by serum creatinine alone and that clinicians should not necessarily be falsely reassured by the latter. Having a more complete picture of kidney health is necessary for proper clinical decision making, for example weighing the risk-benefit ratios of any future interventions which may have nephrotoxic potential.

Furthermore, as proteinuria itself is an important modifiable risk factor, our data suggest that therapies to reduce proteinuria, including blood pressure control and ACE-I or ARB may reduce adverse outcomes after AKI, although these agents appear to be underutilized.[45] Indeed, several new studies[46-48] have suggested that benefits of ACE-I/ARB use following AKI may outweigh the risks. These findings are relevant given the high prevalence of comorbidities with class 1 indications for ACE-I/ARB among patients who experience AKI (eg, diabetes, chronic kidney disease, cardiovascular disease, heart failure). Recent analyses suggest that RAAS inhibition after AKI may not increase risk of recurrent AKI,[49] which is a concern of many clinicians.

Other strengths of our study include the multicenter, prospective study design, and the multiple sensitivity analyses. We were able to take into account risk factors for proteinuria such as concurrently measured blood pressure level, which could not be done in other studies.[12] Because of the matched cohort design, we were able to study prognosis among patients who had AKI in the context of, and in comparison with, patients who did not have AKI during a recent hospitalization to shed insights regarding risk stratification.

Limitations

We acknowledge a number of limitations. The sample size for this prospective cohort study is not as large as reports based on analyzing data collected as part of routine clinical care.[10,12,35] We only included research volunteers, many recruited from academic medical centers and there was no validation cohort. We did not attempt to systematically adjudicate etiology of AKI, capture reasons for hospitalization or measure urine output in our study enrollees. We had a relatively small number of patients with severe AKI, so our results may not be generalizable to those patients. In addition, we do not know how much of the proteinuria observed 3 months after index hospitalization was already present prior to index hospitalization. Because proteinuria is a risk factor for incident AKI[50,51] some of the higher proteinuria observed after AKI was likely present before. However, this does not diminish the fact that post-AKI proteinuria is a key risk discriminant of subsequent loss of renal function. This study also does not address elements of care that occurred between discharge from index hospitalization and 3 months after that may favorably impact downstream loss of kidney function, such as prevention of rehospitalizations, recurrent AKI, or adverse drug events.[52-54] We did not study urine ACR measured at different time points after AKI. Based on this observational study, we are unable to determine if lowering proteinuria after AKI will retard rates of kidney disease progression in the subsequent months to years.

Conclusions

In conclusion, urine ACR measured after AKI is a strong and potentially modifiable risk factor for more rapid loss of renal function. Urine ACR and eGFR measured 3 months after AKI provide key pieces of information to risk stratify patients after AKI, with excellent discrimination. Although AKI and severity of AKI were associated with kidney disease progression, the strengths of associations were greatly attenuated after taking into account urine ACR, eGFR, demographics, and traditional CKD risk factors determined 3 months after hospital discharge. These results together with recently generated data that proteinuria increases after AKI[14,15] point to increased proteinuria (and decreased eGFR) as potentially key steps in the causal pathway linking AKI to CKD. Regardless of the exact pathophysiological connections, proteinuria level is a valuable triage tool post-AKI. Our results suggest there should be more widespread and routine quantification of proteinuria after hospitalized AKI, perhaps similar to how patients with diabetes mellitus undergo screening for proteinuria.[55] This would represent a substantial change from current clinical practice.

ARTICLE INFORMATION

Accepted for Publication: November 1, 2019.

Published Online: January 27, 2020. doi:10.1001/jamainternmed.2019.6390

Author Affiliations: Division of Nephrology, University of California School of Medicine, San Francisco, San Francisco (C.-y. Hsu, Go, R. K. Hsu, Liu); Division of Research, Kaiser Permanente Northern California, Oakland, California (C.-y. Hsu, Go); Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey (Chinchilli); Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York (Coca); Cincinnati Children's Hospital, Division of Nephrology and Hypertension, University of Cincinnati, Cincinnati, Ohio (Devarajan); Division of Nephrology, Department of Medicine, Pennsylvania State University College of Medicine, Hershey (Ghahramani); Vanderbilt Center for Kidney Disease, Division of Nephrology & Hypertension, Vanderbilt University Medical Center, Nashville, Tennessee (Ikizler, Siew); Renal Section, Veterans Affairs New York Harbor Health Care System, New York University School of Medicine, New York (Kaufman); Division of Nephrology, Johns Hopkins

School of Medicine, Baltimore, Maryland (Parikh); University of Texas, Long School of Medicine, San Antonio (Reeves); Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle (Wurfel); Hospital for Sick Children, Division of Nephrology, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada (Zappitelli); Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland (Kimmel); Tennessee Valley Health Services, Nashville Veterans Affairs Hospital, Nashville, Tennessee (Siew).

Author Contributions: All authors had full access to all of the data in the study and Drs C.-y Hsu, Chinchilli, and Siew take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: C.-y Hsu, Devarajan, Ghahramani, Go, R.K. Hsu, Ikizler, Liu, Parikh, Reeves, Zappitelli, Kimmel, Siew.
Acquisition, analysis, or interpretation of data: C.-y Hsu, Chinchilli, Coca, Devarajan, Ghahramani, Go, R.K. Hsu, Ikizler, Kaufman, Liu, Parikh, Wurfel, Zappitelli, Kimmel, Siew.
Drafting of the manuscript: C.-y Hsu, Chinchilli, Go, R.K. Hsu, Wurfel.
Critical revision of the manuscript for important intellectual content: C.-y Hsu, Chinchilli, Coca, Devarajan, Ghahramani, Go, R.K. Hsu, Ikizler, Kaufman, Liu, Parikh, Reeves, Zappitelli, Kimmel, Siew.
Statistical analysis: C.-y Hsu, Chinchilli, Go, R.K. Hsu, Siew.
Obtained funding: C.-y Hsu, Ghahramani, Go, Ikizler, Parikh, Zappitelli.
Administrative, technical, or material support: C.-y Hsu, Devarajan, Go, R.K. Hsu, Kaufman, Parikh, Reeves, Wurfel, Kimmel, Siew.
Supervision: Go, C-y Hsu, Wurfel, Zappitelli, Kimmel.

Conflict of Interest Disclosures: Dr C.-y Hsu reported grants from the National Institutes of Health (NIH) during the conduct of the study. Dr Coca reported personal fees and equity and stock options from RenaltyixAI, personal fees from Takeda, CHF Solutions, Janssen, Goldfinch, Relypsa, and pulseData outside the submitted work. Dr Devarajan is a co-inventor on patents submitted for the use of NGAL as a biomarker of kidney injury, and has licensing agreements with BioPorto, Inc. Dr Ghahramani reported grants from NIH during the conduct of the study. Dr Go reported grants from National Institute of Diabetes, Digestive and Kidney Diseases during the conduct of the study. Dr Ikizler reported personal fees from Fresenius Kabi, Abbott, International Society of Nephrology, and Reata Pharmaceuticals outside the submitted work. Dr Kaufman reported personal fees from National Institute of Diabetes, Digestive and Kidney Disease during the conduct of the study; grant support from Department of Veterans Affairs, Cooperative Studies Program outside the submitted work. Dr Liu reported grants from NIH: National Heart, Lung and Blood Institute, grants from NIH: National Institute of Diabetes and Digestive and Kidney Disease , personal fees from Biomerieux, Durect, Theravance, Quark, Potrero Med, stock holdings from Amgen, travel expenses from National Policy Forum on Critical Care and Acute Renal Failure, travel expenses and speaking fees from Baxter, personal fees from Astra Zeneca, associate editor position at the American Thoracic Society, and personal fees from UpToDate outside the submitted work. Dr Parikh reported Dr. Parikh is a member of the advisory board of RenalytixAI and owns equity in the same. He also serves as consultant for Genfit and TriCeda. Dr Wurfel reported grants from NIDDK during the conduct of the study. Dr Kimmel reported being an Editor with Dr Mark Rosenberg of the textbook Chronic Renal Disease. Dr Siew reported honorarium for an educational talk provided at Da Vita Annual Physician conference February, 2019; consulting for Akebia Therapeutics, Inc; royalties as a contributing author for UptoDate; and being an Associate Editor for the Clinical Journal of the American Society of Nephrology. No other disclosures were reported.

Funding/Support; ASSESS-AKI was supported by cooperative agreements from National Institute of Diabetes and Digestive and Kidney Diseases (U01DK082223, U01DK082185, U01DK082192 and U01DK082183). We also acknowledge funding support from R01DK098233, R01DK101507, R01DK114014, K23DK100468, R03DK111881, and P50DK096418.

ASSESS-AKI Investigators: Study Chair: James Kaufman, MD, New York University School of Medicine; Vernon M. Chinchilli, PhD, Pennsylvania State University; Nasrollah Ghahramani, MD, Pennsylvania State University College of Medicine; W. Brian Reeves, MD, University of Texas; Lan Kong, PhD, Pennsylvania State University; Ming Wang, PhD, Pennsylvania State University; Elana Farace, PhD, Pennsylvania State University (Data Coordinating Center); Alan S Go, MD, University of California, Kaiser Permanente Northern California; Chi-yuan Hsu, MD, University of California, Kaiser Permanente Northern California; Kathleen Liu, MD, University of California; Raymond Hsu, MD, University of California; Thida Tan, MPH, Kaiser Permanente Northern California; Juan D. Ordonez, MD, Kaiser Permanente Northern California; Sijie Zheng, MD, Kaiser Permanente Northern California; T. Alp Ikizler, MD, Vanderbilt University Medical Center; Edward D. Siew, MD, Vanderbilt University Medical Center; Tennessee Valley Health Services; Julia B. Lewis, MD, Vanderbilt University Medical Center; Lorraine Ware, MD, Vanderbilt University Medical Center; Vanderbilt; Chirag Parikh, MD, Johns Hopkins School of Medicine; Steven Coca, DO, Icahn School of Medicine at Mount Sinai; Dennis G. Moledina PhD, Yale; Amit Garg, MD, Western University, Ontario; Prasad Devarajan, MD, University of Cincinnati; Michael Zappitelli, MD, University of Toronto; Jonathan Himmelfarb, MD, University of Washington; Mark Wurfel, MD, University of Washington; Paul L. Kimmel, MD, National Institute of Diabetes, Digestive and Kidney Diseases; Paul W. Eggers, PhD, National Institute of Diabetes and Digestive and Kidney Diseases; and Marva M. Moxey-Mims, MD, Children's National Medical Center.

Disclaimer: The opinions expressed in this article are the authors' own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Additional Contributions: We thank Sophia R.M. Hsu for her technical assistance. She was not compensated.

REFERENCES

1. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*. 2012;81(5):442-448. doi:10.1038/ki.2011.379

2. Hsu RK, Hsu CY. The role of acute kidney injury in chronic kidney disease. *Semin Nephrol*. 2016;36(4):283-292. doi:10.1016/j.semnephrol.2016.05.005

3. Siew ED, Peterson JF, Eden SK, et al. Outpatient nephrology referral rates after acute kidney injury. *J Am Soc Nephrol*. 2012;23(2):305-312. doi:10.1681/ASN.2011030315

4. Koyner JL, Cerdá J, Goldstein SL, et al; Acute Kidney Injury Advisory Group of the American Society of Nephrology. The daily burden of acute kidney injury: a survey of U.S. nephrologists on World Kidney Day. *Am J Kidney Dis*. 2014;64(3):394-401. doi:10.1053/j.ajkd.2014.03.018

5. Goldstein SL, Jaber BL, Faubel S, Chawla LS; Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: a potential opportunity to detect and prevent CKD. *Clin J Am Soc Nephrol*. 2013;8(3):476-483. doi:10.2215/CJN.12101112

6. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int*. 2011;79(12):1361-1369. doi:10.1038/ki.2011.42

7. https://www.niddk.nih.gov/news/meetings-workshops/2019/improving-care-patients-hospitalization-aki. Accessed February 25, 2019.

8. Silver SA, Goldstein SL, Harel Z, et al. Ambulatory care after acute kidney injury: an opportunity to improve patient outcomes. *Can J Kidney Health Dis*. 2015;2:36. doi:10.1186/s40697-015-0071-8

9. Silver SA, Harel Z, Harvey A, et al. Improving care after acute kidney injury: a prospective time series study. *Nephron*. 2015;131(1):43-50. doi:10.1159/000438871

10. James MT, Pannu N, Hemmelgarn BR, et al. Derivation and external validation of prediction models for advanced chronic kidney disease following acute kidney injury. *JAMA*. 2017;318(18):1787-1797. doi:10.1001/jama.2017.16326

11. Stoumpos S, Mark PB, McQuarrie EP, Traynor JP, Geddes CC. Continued monitoring of acute kidney injury survivors might not be necessary in those regaining an estimated glomerular filtration rate >60 mL/min at 1 year. *Nephrol Dial Transplant*. 2017;32(1):81-88.

12. Sawhney S, Marks A, Fluck N, et al. Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury. *Kidney Int*. 2017;92(2):440-452. doi:10.1016/j.kint.2017.02.019

13. Pannu N, James M, Hemmelgarn B, Klarenbach S; Alberta Kidney Disease Network. Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol*. 2013;8(2):194-202. doi:10.2215/CJN.06480612

14. Parr SK, Matheny ME, Abdel-Kader K, et al. Acute kidney injury is a risk factor for subsequent proteinuria. *Kidney Int*. 2018;93(2):460-469. doi:10.1016/j.kint.2017.07.007

15. Hsu CY, Hsu RK, Liu KD, et al. Impact of acute kidney injury on urinary protein excretion: analysis of two prospective cohorts (ASSESS-AKI and CRIC). *J Am Soc Nephrol*. 2019;30(7):1271-1281. doi:10.1681/ASN.2018101036

16. Landray MJ, Emberson JR, Blackwell L, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis*. 2010;56(6):1082-1094. doi:10.1053/j.ajkd.2010.07.016

17. Tangri N, Grams ME, Levey AS, et al; CKD Prognosis Consortium. Multinational assessment of accuracy of equations for predicting risk of kidney failure: A meta-analysis. *JAMA*. 2016;315(2):164-174. doi:10.1001/jama.2015.18202

18. Hsu CY, Xie D, Waikar SS, et al; CRIC Study Investigators; CKD Biomarkers Consortium. Urine biomarkers of tubular injury do not improve on the clinical model predicting chronic kidney disease progression. *Kidney Int*. 2017;91(1):196-203. doi:10.1016/j.kint.2016.09.003

19. Horne KL, Packington R, Monaghan J, Reilly T, Selby NM. Three-year outcomes after acute kidney injury: results of a prospective parallel group cohort study. *BMJ Open*. 2017;7(3):e015316. doi:10.1136/bmjopen-2016-015316

20. Go AS, Parikh CR, Ikizler TA, et al; Assessment Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury Study Investigators. The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. *BMC Nephrol*. 2010;11:22. doi:10.1186/1471-2369-11-22

21. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006

22. Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31. doi:10.1186/cc5713

23. Yang W, Xie D, Anderson AH, et al; CRIC Study Investigators. Association of kidney disease outcomes with risk factors for CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2014;63(2):236-243. doi:10.1053/j.ajkd.2013.08.028

24. Liu KD, Yang W, Anderson AH, et al; Chronic Renal Insufficiency Cohort (CRIC) study investigators. Urine neutrophil gelatinase-associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease. *Kidney Int*. 2013;83(5):909-914. doi:10.1038/ki.2012.458

25. Parsa A, Kao WH, Xie D, et al; AASK Study Investigators; CRIC Study Investigators. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med*. 2013;369(23):2183-2196. doi:10.1056/NEJMoa1310345

26. Lambers Heerspink HJ, Tighiouart H, Sang Y, et al. GFR decline and subsequent risk of established kidney outcomes: a meta-analysis of 37 randomized controlled trials. *Am J Kidney Dis*. 2014;64(6):860-866. doi:10.1053/j.ajkd.2014.08.018

27. Brenner BM, Cooper ME, de Zeeuw D, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-869. doi:10.1056/NEJMoa011161

28. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860. doi:10.1056/NEJMoa011303

29. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329(20):1456-1462. doi:10.1056/NEJM199311113292004

30. Cox DR. Regression models and life-tables (with discussion). *J R Stat Soc B*. 1972;34:187-220.

31. Gonen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. *Biometrika*. 2005;92:965-970. doi:10.1093/biomet/92.4.965

32. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med*. 2009;169(4):342-350. doi:10.1001/archinternmed.2008.605

33. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA*. 2011;305(15):1553-1559. doi:10.1001/jama.2011.451

34. Grams ME, Sang Y, Coresh J, et al. Candidate surrogate end points for ESRD after AKI. *J Am Soc Nephrol*. 2016;27(9):2851-2859. doi:10.1681/ASN.2015070829

35. Sawhney S, Beaulieu M, Black C, et al. Predicting kidney failure after acute kidney injury among people receiving nephrology clinic care [published online October 15, 2018]. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfy294

36. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172. doi:10.1002/sim.2929

37. Karsanji DJ, Pannu N, Manns BJ, et al. Disparity between nephrologists' opinions and contemporary practices for community follow-up after AKI hospitalization. *Clin J Am Soc Nephrol*. 2017;12(11):1753-1761. doi:10.2215/CJN.01450217

38. Kirwan CJ, Blunden MJ, Dobbie H, James A, Nedungadi A, Prowle JR. Critically ill patients requiring acute renal replacement therapy are at an increased risk of long-term renal dysfunction, but rarely receive specialist nephrology follow-up. *Nephron*. 2015;129(3):164-170. doi:10.1159/000371448

39. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Chapter 2.5: Diagnostic approach to alterations in kidney function and structure. *Kidney Int Suppl*. 2012;2:33-36.

40. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371(1):58-66. doi:10.1056/NEJMra1214243

41. Healthy People 2020. https://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease/objectives. Accessed July 3, 2017.

42. Matheny ME, Peterson JF, Eden SK, et al. Laboratory test surveillance following acute kidney injury. *PLoS One*. 2014;9(8):e103746. doi:10.1371/journal.pone.0103746

43. 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(6):833-841. doi:10.2215/CJN.12591117

44. Bansal N, Matheny ME, Greevy RA Jr, et al. Acute kidney injury and risk of incident heart failure among US veterans. *Am J Kidney Dis*. 2018;71(2):236-245. doi:10.1053/j.ajkd.2017.08.027

45. Leung KCW, Pannu N, Tan Z, et al; APPROACH and AKDN Investigators. Contrast-associated AKI and use of cardiovascular medications after acute coronary syndrome. *Clin J Am Soc Nephrol*. 2014;9(11):1840-1848. doi:10.2215/CJN.03460414

46. Chou YH, Huang TM, Pan SY, et al. Renin-angiotensin system inhibitor is associated with lower risk of ensuing chronic kidney disease after functional recovery from acute kidney injury. *Sci Rep*. 2017;7:46518. doi:10.1038/srep46518

47. Gayat E, Hollinger A, Cariou A, et al; FROG-ICU investigators. Impact of angiotensin-converting enzyme inhibitors or receptor blockers on post-ICU discharge outcome in patients with acute kidney injury. *Intensive Care Med*. 2018;44(5):598-605. doi:10.1007/s00134-018-5160-6

48. Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Pannu N; Interdisciplinary Chronic Disease Collaboration. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. *JAMA Intern Med*. 2018;178(12):1681-1690. doi:10.1001/jamainternmed.2018.4749

49. Hsu CY, Liu KD, Yang J, et al. Renin-angiotensin system blockade after acute kidney injury (AKI) and risk of recurrent AKI [published online December 16, 2019]. *Clin J Am Soc Nephrol*. doi:10.2215/CJN.05800519

50. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int*. 2008;74(1):101-107. doi:10.1038/ki.2008.107

51. Hsu RK, Hsu CY. Proteinuria and reduced glomerular filtration rate as risk factors for acute kidney injury. *Curr Opin Nephrol Hypertens*. 2011;20(3):211-217. doi:10.1097/MNH.0b013e3283454f8d

52. Silver SA, Harel Z, McArthur E, et al. 30-day readmissions after an acute kidney injury hospitalization. *Am J Med*. 2017;130(2):163-172.e4. doi:10.1016/j.amjmed.2016.09.016

53. Siew ED, Parr SK, Abdel-Kader K, et al. Predictors of Recurrent AKI. *J Am Soc Nephrol*. 2016;27(4):1190-1200. doi:10.1681/ASN.2014121218

54. Hung AM, Siew ED, Wilson OD, et al. Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. *Diabetes Care*. 2018;41(3):503-512. doi:10.2337/dc17-1237

55. American Diabetes Association. Microvascular complications and foot care: *Standards of Medical Care in Diabetes-2019*. *Diabetes Care*. 2019;42(suppl 1):S124-S138. doi:10.2337/dc19-S011