A comprehensive description of kidney disease progression after acute kidney injury from a prospective, parallel-group cohort study

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Acute kidney injury (AKI) is associated with adverse long-term outcomes, but many studies are retrospective, focused on specific patient groups or lack adequate comparators. The ARID (AKI Risk in Derby) Study was a five-year prospective parallel-group cohort study to examine this. Hospitalized cohorts with and without exposure to AKI were matched 1:1 for age, baseline kidney function, and diabetes. Estimated glomerular filtration rate (eGFR) and the urinary albumin:creatinine ratio (uACR) were measured at three-months, one-, three- and five-years. Outcomes included kidney disease progression, heart failure episodes and mortality. In 866 matched individuals, kidney disease progression at five years was found to be significantly increased in 30% of the exposed group versus 7% of those non-exposed (adjusted odds ratio 2.49 [95% confidence interval 1.43 to 4.36]). In the AKI group, this was largely characterized by incomplete recovery of kidney function by three months. Further episodes of AKI during follow-up were significantly more common in the exposed group (odds ratio 2.71 [1.94 to 3.77]) and had an additive effect on risk of kidney disease progression. Mortality and heart failure episodes were more frequent in the exposed group, but the association with AKI was no longer significant when models were adjusted for three-month eGFR and uACR. In a general hospitalized population, kidney disease progression after five years was common and strongly associated with AKI. Thus, the time course of changes and the attenuation of associations with adverse outcomes after adjustment for three-month eGFR and uACR suggest non-recovery of kidney function is an important assessment in post-AKI care and a potential future target for intervention.

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Lay Summary

Acute kidney injury (AKI) is a sudden decline in kidney function, which is a common problem in people admitted to hospital. AKI has been linked to serious long-term problems for patients, but there are few studies that identify a wide range of people shortly after AKI and closely monitor them thereafter. The Acute Kidney Injury Risk in Derby study recruited 2 groups of people who had recently been in hospital and monitored them for 5 years. One group had AKI, and the other did not. Comparing the 2 groups, we found that worsening kidney health, admission for heart failure, and death were all more common in the group who had AKI at the start of the study. Our results suggested that some people do not fully recover kidney health after AKI. This is important to guide assessment and care for people after AKI.

Acute kidney injury (AKI) is common and increasing among hospitalized populations.[1] In addition to poor short-term outcomes, studies have demonstrated that AKI is associated with longer-term adverse effects including increased mortality, development of chronic kidney disease (CKD), and cardiovascular events.[2] However, previous work in this area is predominantly retrospective, leaving many studies susceptible to increased risk of confounding and ascertainment bias. In addition, lack of standardized timed follow-up assessments prevents clear descriptions of the patterns of changes in kidney function after AKI and the mechanisms by which these may occur.[3]

More recently, the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury Study confirmed

this increased risk of CKD after AKI in a large prospective US study.[4] The study population comprised patients from 4 cohorts, which included specific patient groups such as critical care and cardiothoracic surgery. Reported outcomes include associations between AKI and subsequent CKD and between 3-month albuminuria in AKI survivors and clinical outcomes.[4,5] Performed at a similar time, the Acute Kidney Injury Risk in Derby (ARID) study is a UK-based prospective cohort study that was also designed to examine the long-term effects of AKI. Similarities exist between the ARID and Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury study designs, but key differences in the ARID study include its European population and a focus almost entirely on general hospital (ward-level) patients. Here, we report a comprehensive description of the 5-year outcomes from the ARID study, with specific focus on the natural history of CKD after AKI.

METHODS

Study design, setting, and participants

The ARID study is a prospective matched cohort study designed to report long-term outcomes after AKI. Between May 2013 and May 2016, the study recruited 2 cohorts of people hospitalized at the Royal Derby Hospital, Derby, UK, who had survived at least 90 days after hospital admission. One cohort consisted of people who had developed AKI during hospital admission (exposed group), and the second cohort had not (non-exposed group). After recruitment, exposed and non-exposed participants were matched 1:1 for baseline estimated glomerular filtration rate (eGFR) stage (eGFR $>$ 60 ml/min per 1.73 m^2, eGFR stages 3A, 3B, or 4), age ($\pm$5 years), and diabetes. Approvals for the study were obtained from the Derbyshire Research Ethics Committee and the National Information Governance Board. All participants provided written informed consent.

Participants were eligible if they were aged between 18 and 85 years, had at least 1 inpatient serum creatinine measurement, and baseline creatinine within the preceding 12 months. Potential participants were identified through automated screening of serum creatinine laboratory results, as previously described.[6,7] The presence of AKI was determined according to serum creatinine components of the Kidney Disease: Improving Global Outcomes criteria.[8] The baseline creatinine value was taken as the most recent stable serum creatinine before hospital admission. Urine output was not used to define AKI because of its inaccurate recording in a general hospitalized population. Other exclusion criteria were total or partial nephrectomy during index admission, preexisting CKD stage G5, or receiving palliative care.

All AKI episodes were adjudicated by a member of the research team to confirm the presence of AKI, Kidney Disease: Improving Global Outcomes stage, and duration (in days). Etiology of AKI was determined by manual review of electronic patient records. The biochemistry results of participants in the non-exposed group were also individually reviewed to confirm that they had not sustained AKI during their index hospital stay.

Procedures

Serum creatinine, eGFR (2009 Chronic Kidney Disease Epidemiology Collaboration Equation), and albuminuria were measured at 3 months, 1 year, 3 years, and 5 years after the index blood test. For the exposed group, this was the day of AKI onset; and for the non-exposed group, this was the first blood test at admission. Participants were asked not to eat cooked meat for at least 12 hours before giving a blood sample and were asked to provide an early morning urine specimen. Samples were handled separately from routine clinical samples with rapid transfer and analysis within 7 hours in the central hospital laboratory. In addition to absolute eGFR values, the annualized eGFR trajectory (ml/min per 1.73 m^2 per year) between data collection points was calculated for each individual. Demographics, hospital admission data, Charlson index score, inpatient laboratory test results, and coded comorbidities were extracted from the hospital electronic medical record.

Outcomes

The following clinical end points were compared between exposed and non-exposed groups: kidney disease progression, mortality, and heart failure episodes. The maximum follow-up for all outcomes was 5 years. *Kidney disease progression* was defined as a decrease in eGFR of $\geq$25% associated with a decline in eGFR stage.[9,10] This definition was used both in individuals with known CKD at baseline and in those with baseline eGFR $>$ 60 ml/min per 1.73 m^2. A combined kidney end point of doubling of serum creatinine, commencement of kidney replacement therapy (KRT), or eGFR $<$ 15 ml/min per 1.73 m^2 was also recorded. Individuals who had a progression to the combined renal end point were also classed as having shown kidney disease progression. *Albuminuria* was defined as urine albumin-creatinine ratio (ACR) $\geq$ 3.0 mg/mmol. Cross-referencing with the local renal database was used to track the commencement of long-term KRT. Mortality and hospital readmission data including heart failure episodes were taken from the electronic medical record.

Statistical analysis

Statistical analyses were performed using the statistical software SPSS version 25.0 (IBM Corporation) and SAS OnDemand for Academics (SAS Institute). Continuous variables are presented as mean $\pm$ SD or median (interquartile range), while categorical variables are presented as count (percentage). Paired *t* test and Wilcoxon test were used for intragroup comparisons for continuous variables. Student *t* test and Mann-Whitney *U* test were used for intergroup comparisons for continuous variables and chi-square test and Fisher exact test for categorical variables. Kaplan-Meier survival curves and Cox regression analysis were used to examine mortality and heart failure episodes. Multivariable modeling was conducted to identify independent predictors of kidney disease progression. Each potential predictor variable was analyzed independently to identify those with significant association (cutoff $P = 0.25$ so that all potentially important variables were included in the modeling) and then successive binary logistic regression performed with the most insignificant variables removed stepwise until only statistically significant variables remained ($P < 0.05$) on the basis of *P* values, pseudo-R^2 values, and model prediction strength. Model assumptions were checked using the Box-Tidwell test. A competing risk analysis was performed using the Fine-Gray subdistribution hazards model[11] to calculate the cumulative incidence function, accounting for the competing risk of death and significant covariables. The midpoint of the time period in which kidney disease progression first occurred was used when classifying participants with respect to this outcome.

RESULTS

Participant characteristics

A total of 1125 participants were recruited, of whom 1010 were suitable for matching. A total of 866 participants were matched, with 433 participants each in the exposed and non-exposed groups. Participant recruitment and follow-up are shown in Figure 1. At 5 years, the lost to follow-up rate was low at 3.3% (12 participants from the exposed group and 17 from the non-exposed group).

The baseline characteristics of the 866 participants are listed in Table 1. Matching was good with few differences between the exposed and non-exposed groups. In particular, the proportion of participants with diabetes and preexisting CKD and who those were past or current smokers were the same between groups. A higher proportion of participants in the exposed group were taking renin-angiotensin-aldosterone system inhibitors and nonsteroidal anti-inflammatory agents at the time of hospital admission.

Hospital stay data for each group are presented in Table 2. The exposed group had a longer hospital stay and more frequent rates of admission to the intensive care unit during index admission, although the latter was uncommon (3.3% across the whole group). AKI was most commonly stage 1 (59% in the exposed group), and only 5 participants required acute KRT.

Kidney disease progression and its predictors

Kidney disease progression was significantly more common at all time points in those exposed to AKI during index admission than those in the non-exposed group (3 months: 17% vs. 3%; 1 year: 24% vs. 4%; 3 years: 27% vs. 7%; and 5 years: 30% vs. 7%; $P < 0.001$ for all comparisons between groups). This association was seen both in participants with known preexisting CKD at baseline (44% vs. 12%; $P < 0.001$) and in those with baseline eGFR $>$ 60 ml/min per 1.73 m^2 (24% vs. 5%; $P < 0.001$). The mean eGFR was significantly lower in the exposed group at all time points other than baseline (Figure 2).

Table 3 summarizes the independent associations with kidney disease progression at 5 years and associated adjusted odds ratios (ORs) from binary logistic regression analyses. A full list of univariable associations with kidney disease progression is presented in Supplementary Table S1, and association of AKI duration on kidney disease progression is described in Supplementary Table S2. In the multivariable model, AKI, diabetes, gender, Charlson index score, change in eGFR from baseline to 3 months (delta eGFR), and albuminuria at 3 months were independent predictors of 5-year kidney disease progression. AKI was associated with kidney disease progression at 5 years in the unadjusted model (OR 5.65; 95% confidence interval [CI] 3.49–9.13; $P < 0.0001$) and remained so in the adjusted model (OR 2.47; 95% CI 1.39–4.40; $P = 0.002$).

We sought to test this finding with several sensitivity analyses. We repeated the binary logistic regression after using propensity score matching to derive the exposed and non-exposed groups, and AKI remained an independent predictor of kidney disease progression with a similar adjusted OR (2.15; 95% CI 1.25–3.71); the demographics of the propensity matched groups and results of comparisons are presented in Supplementary Tables S3 and S4.

We also performed further analysis to account for the competing risk of death on the incidence of kidney disease progression. The cumulative incidence function calculated using the Fine-Gray subdistribution hazards model confirmed the increased probability of kidney disease progression in the AKI group after accounting for mortality during follow-up, adjusted for 3-month albuminuria, 3-month delta eGFR, Charlson index

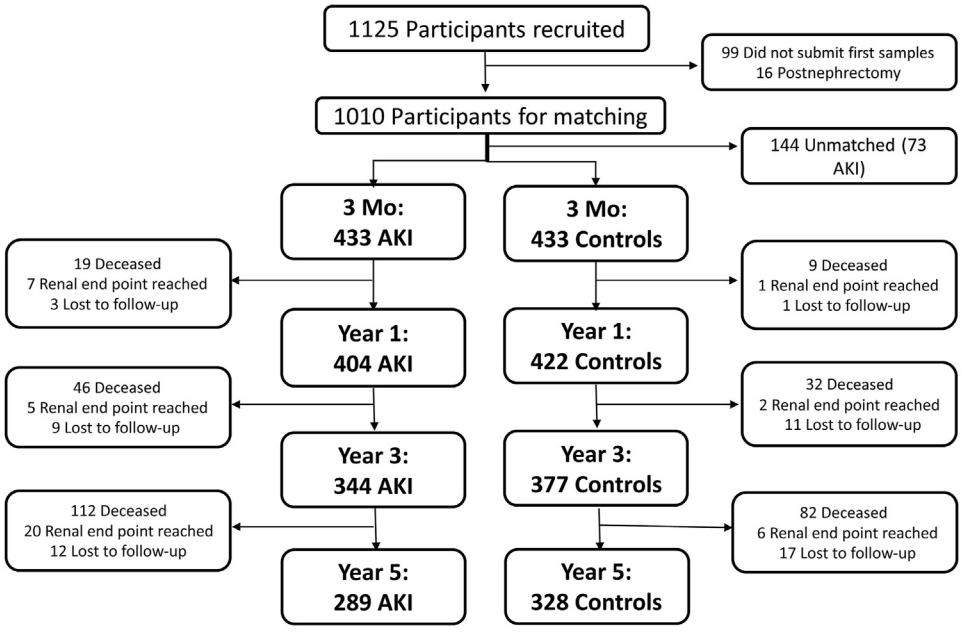


Figure 1 | Consort diagram showing participants flow through the Acute Kidney Injury (AKI) Risk in Derby (ARID) study.

Table 1 | Baseline participant characteristics in the exposed and non-exposed groups

Variable	Exposed (AKI) group (n = 433)	Non-exposed (control) group (n = 433)	P[a]
Age, yr	69.6 ± 10.1	69.7 ± 9.8	
Male gender	248 (57)	221 (51)	0.07
White ethnicity	412 (95)	397 (92)	0.1
Smoking status			
Never	160 (41)	166 (42)	
Past	194 (50)	211 (53)	
Current	35 (9)	21 (5)	0.1
Charlson index score	1 (0–2)	0 (0–2)	0.001
Baseline eGFR, ml/min per 1.73 m^2	69.6 ± 20	70.3 ± 20	
Baseline eGFR stage, ml/min per 1.73 m^2			
>90	72 (17)	72 (17)	
60–90	235 (54)	234 (54)	
45–59	82 (19)	83 (19)	
30–44	31 (7)	31 (7)	
15–29	13 (3)	13 (3)	
Diabetes	94 (22)	94 (22)	
Ischemic heart disease	44 (10)	42 (10)	0.8
Cerebrovascular disease	4 (1)	4 (1)	1.0
Peripheral vascular disease	15 (4)	11 (3)	0.4
Heart failure	35 (8)	25 (6)	0.2
Liver disease	3 (1)	1 (0.2)	0.3
Chronic lung disease	65 (15)	81 (19)	0.2
Cancer	27 (6)	23 (5)	0.6

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Exposed vs. non-exposed.
Data are expressed as mean ± SD, median (IQR), or n (%).

Table 2 | Details of index hospital admission in the exposed (AKI) and non-exposed (non-AKI) groups

Variable	Exposed group (n = 433)	Non-exposed group (n = 433)	P[a]
Length of stay, d	7 (4–12)	5 (3–8)	<0.001
ICU admission	25 (6)	4 (1)	<0.001
Received iodinated contrast	85 (20)	108 (25)	0.06
NSAID at admission	51 (12)	28 (7)	0.007
ACEi/ARB at admission	222 (51)	170 (39)	<0.001
Diuretic at admission	141 (33)	122 (28)	0.16
Metformin at admission	49 (11)	43 (10)	0.5
Statin at admission	201 (46)	191 (44)	0.5
Details of AKI			
Severity			
Stage 1	255 (59)		
Stage 2	106 (24)		
Stage 3	72 (17)		
Duration, d	3 (2–5)		
AKD	77 (18)		
Community-acquired AKI	271 (63)		
Required KRT for AKI	5 (1)		

ACEi, angiotensin-converting enzyme inhibitor; AKD, acute kidney disease; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; ICU, intensive care unit; IQR, interquartile range; KRT, kidney replacement therapy; NSAID, nonsteroidal anti-inflammatory drug.
[a]Exposed vs. non-exposed.
Data are expressed as mean ± SD, median (IQR), or n (%).

score, and age (Table 4). Details of the cumulative incidence function model are provided in Supplementary Figure S1.

Furthermore, we compared eGFR slope (calculated individually from baseline and timed follow-up samples, but excluding inpatient values) between groups over the 5-year follow-up period and the median eGFR slope in the AKI group was significantly more negative than that in the non-exposed group (Supplementary Table S5).

Development of advanced CKD

The numbers reaching the combined kidney end point (doubling of serum creatinine, eGFR < 15 ml/min per 1.7 3 m^2, or KRT) within 5 years were low, although significantly higher in the exposed group (20 [5%] vs. 6 [1%]; $P = 0.005$). Of those reaching the combined renal end point, 9 commenced KRT for kidney failure, of whom 6 were in the exposed group. The median time from index hospitalization to start of KRT was 634 days (interquartile range 313–1247 days). Although the numbers are small, the most ostensible feature in those who reached the combined kidney end point was worse baseline kidney function. In the 9 who commenced KRT, the mean baseline eGFR was 28 ± 11 ml/min per 1.73 m^2 and all had preexisting CKD (5 had CKD stage G4, 3 CKD stage G3B, and 1 CKD stage G3A). Further details are provided in Supplementary Table S6.

Time course of changes in renal function

In the AKI group, the eGFR trajectory was not constant across the 5-year follow-up period. The most significant change in eGFR trajectory, and the biggest difference between exposed and non-exposed groups, was between baseline and 3-month time points (a significant interaction between exposure and time period was observed; $P < 0.001$). These data are summarized in Figure 3. Between baseline and 3 months, the annualized eGFR trajectory was −20.5 ± 44.3 ml/min per 1.73 m^2 per year in the exposed group whereas there was an apparent increase in eGFR of +9.9 ± 40.2 ml/min per 1.73 m^2 per year in the non-exposed group ($P < 0.001$). In contrast, the rates of change were smaller and there was no significant difference in eGFR trajectories between the 2 groups from 3 months to 1 year, from 1 year to 3 years, and from 3 years to 5 years.

Albuminuria and effect on CKD classification

Albuminuria (ACR ≥ 3 mg/mmol) was more common in the exposed group at each time point. At 3 months, 180 individuals (42%) in the exposed group had albuminuria compared with 100 (23%) in the non-exposed group ($P < 0.001$). The distribution according to albuminuria category is provided in Table 5.

At 5 years, 90 of those (29%) in the exposed group who were alive had albuminuria, 177 (57%) did not have albuminuria, and 41 (13%) had missing data (this group includes those who had a progression to kidney failure). Comparative numbers in the non-exposed group were 65 (19%) with albuminuria, 234 (67%) without albuminuria, and 49 (14%)

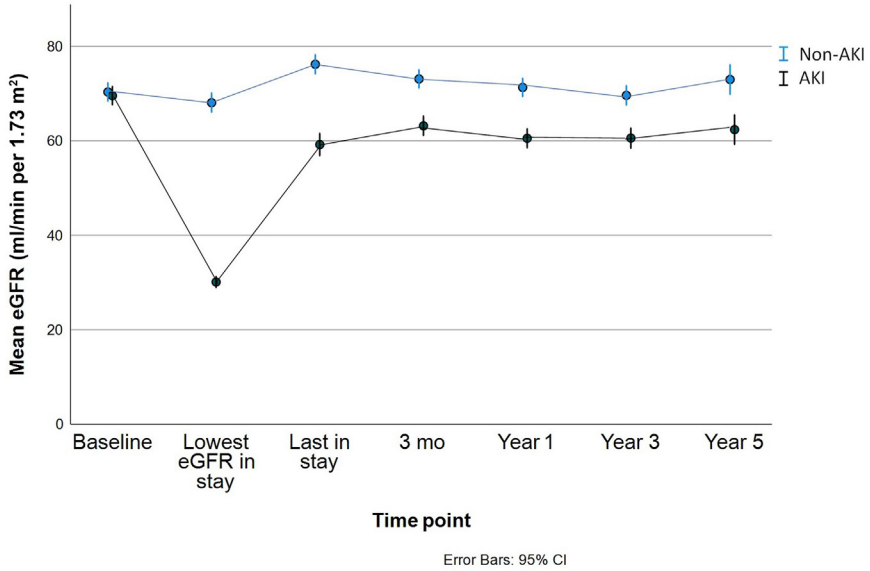


Figure 2 | Mean estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2) at different time points in the study comparing exposed and non-exposed groups. The mean eGFR at baseline was 69.6 ± 20.4 ml/min per 1.73 m^2 (acute kidney injury [AKI]) versus 70.4 ± 20.3 ml/min per 1.73 m^2 (non-AKI); lowest during index hospital stay 30.1 ± 12.4 ml/min per 1.73 m^2 versus 68.1 ± 21.2 ml/min per 1.73 m^2; last during index hospital stay 59.2 ± 24.7 ml/min per 1.73 m^2 versus 76.2 ± 21.3 ml/min per 1.73 m^2; 3 months 63.2 ± 21.6 ml/min per 1.73 m^2 versus 73.1 ± 20.4 ml/min per 1.73 m^2; 1 year 60.5 ± 20.4 ml/min per 1.73 m^2 versus 71.3 ± 20 ml/min per 1.73 m^2; 3 years 60.6 ± 20.1 ml/min per 1.73 m^2 versus 69.6 ± 20.3 ml/min per 1.73 m^2; and 5 years 62.4 ± 27.7 ml/min per 1.73 m^2 versus 73 ± 29 ml/min per 1.73 m^2. $P = 0.6$ for comparison at baseline, $P < 0.0001$ for all other comparisons between groups.

with missing data. The proportion with albuminuria was significantly different between groups ($P < 0.001$). At 5 years, using albuminuria in addition to eGFR to apply the Kidney Disease: Improving Global Outcomes CKD criteria to the cohort led to more individuals meeting the criteria for CKD diagnosis. A total of 157 individuals (51%) in the exposed group and 95 (27%) in the non-exposed group met eGFR-only criteria (eGFR < 60 ml/min per 1.73 m^2) at 5 years. The number categorized as having CKD if both eGFR and albuminuria criteria were applied was 180 (58%) in the exposed group and 110 (32%) in the non-exposed group.

Episodes of AKI during follow-up

In the exposed group, 138 participants (34%) had at least 1 further episode of AKI during follow-up versus 67 (16%) in the non-exposed group (OR 2.71; 95% CI 1.94–3.77; $P < 0.001$). The follow-up period in which AKI episodes occurred is presented in Supplementary Table S7. Independent associations with the development of AKI during the follow-up period are presented in Table 6. Binary logistic regression, including all matched participants, showed that AKI during follow-up was independently associated with kidney disease progression at 5 years after adjustment for baseline eGFR, AKI during index admission, diabetes, gender, 3-month albuminuria, and delta eGFR at 3 months (OR 2.49; 95% CI 1.42–4.37; $P = 0.002$).

Further, there was a cumulative effect of additional episodes of AKI, in that the proportion with kidney disease progression at 5 years was the highest among those who had AKI both during index admission and during follow-up. Proportions with kidney disease progression were similar between the exposed group without AKI during follow-up and the comparator group of patients who did have AKI during follow-up, with significantly lower numbers in those who never had AKI. These data are presented in Figure 4. In addition, the number of time periods in which AKI occurred during follow-up was an independent predictor of 5-year kidney disease progression when adjusted for AKI during

Table 3 | Factors associated with kidney disease progression at 5 yr using binary logistic regression

Analysis group	Variable	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Whole cohort	AKI	5.65 (3.49–9.13)	<0.001	2.47 (1.39–4.40)	0.002
	Female gender	0.54 (0.36–0.81)	0.002	0.57 (0.34–0.97)	0.04
	Diabetes	2.49 (1.59–3.89)	<0.001	2.10 (1.14–3.89)	0.02
	Charlson index score	1.49 (1.30–1.70)	<0.001	1.06 (0.88–1.28)	0.5
	3-Mo albuminuria	4.05 (2.66–6.15)	<0.001	2.58 (1.50–4.42)	<0.001
	3-Mo delta eGFR	0.89 (0.87–0.91)	<0.001	0.89 (0.86–0.91)	<0.001
	Age	1.03 (1.01–1.05)	0.01	1.00 (0.97–1.03)	0.9
	Baseline eGFR	0.98 (0.97–0.99)	<0.001	0.97 (0.96–0.99)	<0.001

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

Table 4 | Subdistribution HR of variables included in the Fine-Gray model, which models the probability of kidney disease progression at 5 yr accounting for the competing risk of mortality[a]

Variable	Subdistribution HR (95% CI)	P
AKI	2.456 (1.655–3.646)	<0.001
Age	1.019 (0.998–1.041)	0.07
Female gender	0.793 (0.558–1.126)	0.2
Diabetes	1.048 (0.703–1.562)	0.8
Baseline eGFR	0.980 (0.970–0.99)	<0.001
Charlson index score	1.078 (0.967–1.201)	0.2
Change in eGFR from baseline to 3 mo	0.929 (0.911–0.947)	<0.001
Albuminuria	1.397 (0.968–2.016)	0.07

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]The subdistribution HR for variables included in the Fine-Gray model demonstrates the direct impact of the variable on the cumulative incidence function. A value of >1 is interpreted as increasing the risk of experiencing the outcome, and if the value is greater than that of a different variable, it has a more significant impact than that variable. However, the magnitude of impact is unknown.

index admission, 3-month albuminuria, and Charlson index score (adjusted OR 1.849; 95% CI 1.350–2.530; $P < 0.001$).

Mortality

Over the 5-year follow-up period, mortality was higher in the exposed group (26%) than in the non-exposed group (19%) ($P = 0.014$). Kaplan-Meier analysis (Figure 5) showed that survival time was shorter in the exposed group (1587 ± 23 days in the exposed group vs. 1668 ± 18 days in the non-exposed group; log rank 6.42; $P = 0.01$). The increased hazard ratio in the exposed group persisted when adjusted for age, baseline eGFR, comorbidity, smoking history, and diabetes. However, the association of AKI and mortality was reduced and no longer significant when adjusted for albuminuria and delta eGFR at 3 months (Table 7).

Table 5 | Albuminuria levels measured 3 mo after index hospitalization[a]

3-Mo albuminuria measurement	Exposed group ($n = 432$)	Non-exposed group ($n = 429$)	P
ACR <3 mg/mmol	252 (58)	330 (77)	<0.001
ACR 3–30 mg/mmol	129 (30)	81 (19)	<0.001
ACR >30–300 mg/mmol	51 (12)	18 (4)	<0.001
Median ACR at 3 mo (mg/mmol)	1.8 (0.6–9.4)	0.8 (0.1–2.8)	<0.001

ACR, albumin-creatinine ratio; IQR, interquartile range.
[a]Only participants with proteinuria data available included in total numbers. Data are expressed as median (IQR) or n (%).

Incidence of heart failure

In the exposed group, 90 individuals (21%) had at least 1 episode of heart failure requiring hospitalization compared with 67 (16%) in the non-exposed group ($P = 0.042$). Kaplan-Meier survival analysis showed that mean time to heart failure events was shorter in the exposed group than in the non-exposed group (1589 ± 24 days in the exposed group vs. 1657 ± 22 days in the non-exposed group; log rank 4.87; $P = 0.03$) (Figure 5). Again, an increased hazard ratio in the exposed group was seen after adjusting for age, diabetes, baseline eGFR, and smoking history, but was reduced and no longer significant when adjusted for albuminuria and delta

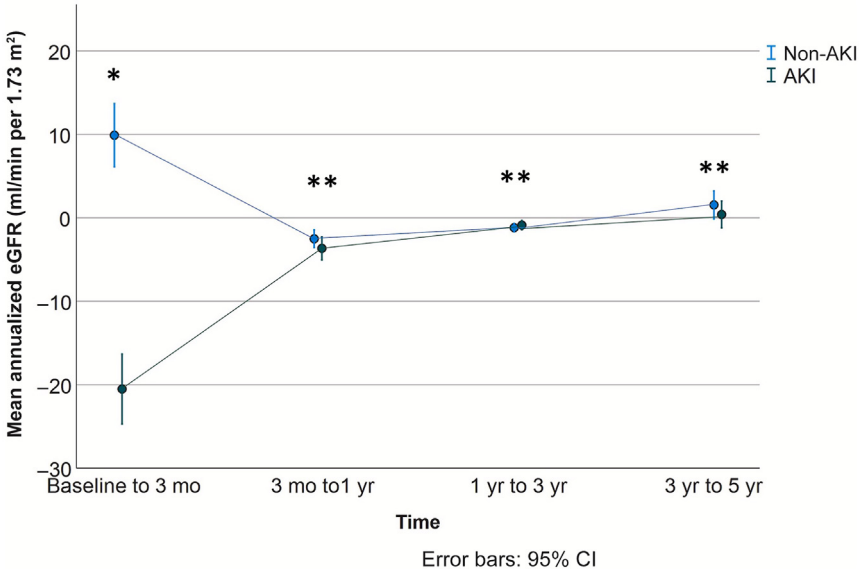


Figure 3 | Annualized estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2 per year) between follow-up time points after hospital admission, comparing exposed and non-exposed groups. Comparisons between exposed and non-exposed groups: *$P < 0.0001$, **$P \geq 0.1$. Within-group differences between time periods were significant for comparisons of the baseline to 3-month period with later time periods ($P < 0.0001$ for all comparisons in both groups) and of the 3-month to 1-year period with the 1-year to 3-year period only in the acute kidney injury (AKI) group ($P = 0.02$). No significant differences were observed in either group comparing the 1-year to 3-year period with the 3-year to 5-year period ($P = 0.7$ for the exposed group and $P = 0.6$ for the non-exposed group).

Table 6 | Independent associations with developing AKI during the follow-up period

Variable	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
AKI during index admission	2.705 (1.940–3.772)	<0.001	2.146 (1.467–3.140)	<0.001
Baseline eGFR	0.975 (0.967–0.983)	<0.001	0.980 (0.970–0.989)	<0.001
Current or past smoker	1.470 (1.043–2.074)	0.03	1.614 (1.106–2.356)	0.01
Hemoglobin at 3 mo	0.975 (0.965–0.985)	<0.001	0.983 (0.972–0.995)	0.004
Albuminuria at 3 mo	3.157 (2.273–4.386)	<0.001	2.060 (1.409–3.012)	<0.001

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

eGFR at 3 months or recurrent AKI (Table 7). Similar patterns were seen with total cardiovascular events (Supplementary Figure S2 and Supplementary Table S8).

DISCUSSION

We have demonstrated increased incidence of kidney disease progression, recurrent AKI, heart failure admissions, and mortality after AKI compared to a well-matched comparator group over 5 years of prospective follow-up. Kidney disease progression occurred in almost a third of those who had developed AKI, although the proportion who developed kidney failure was much lower. Assessment for albuminuria increased the proportion with CKD, and to a greater extent in those who had been exposed to AKI. Nonrecovery of kidney function and albuminuria at 3 months as well as subsequent episodes of AKI appear to be important determinants of subsequent heart failure and mortality.

It is well recognized that AKI is associated with long-term adverse patient outcomes, including higher mortality and development of CKD. These associations have been described in many studies and systematic reviews.[2,12,13] However, a recent systematic review showed how the majority of studies in this area are retrospective in design (77% of the included studies comprising 96.5% of the pooled patients), 50% were from the intensive care unit or cardiac surgery settings, and none incorporated albuminuria in their definition of CKD.[3,13] Prospective studies with a lower risk of residual confounding and with protocolized follow-up are therefore valuable to confirm these associations, but also to provide new information on the natural history of the long-term sequelae of AKI.

Our results confirm that kidney disease progression was strongly and independently associated with AKI, both in those with normal premorbid kidney function and in those with preexisting CKD. The strength of this association was shown in multivariable and competing risk analyses. In addition, there was an additive effect of multiple AKI episodes on the risk of kidney disease progression at 5 years, which strengthens the argument that AKI is causally related to subsequent CKD. These findings are consistent with those from the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury Study, which reported similar magnitudes of increased adjusted hazard ratios of CKD incidence (3.98) and CKD progression (2.37) after AKI[5] and that 3-month albuminuria was an independent risk factor for subsequent kidney disease progression.[4] Our results also showed that 3-month albuminuria and delta eGFR were independently associated with kidney disease progression at 5 years, along with diabetes, gender, and comorbidity score. As the ARID study reflects AKI in a general ward–based setting, in which 60% of cases had AKI stage 1, our results emphasize the importance of post-discharge AKI care in which measuring eGFR and urinary ACR at 3 months provides important information on future risk.

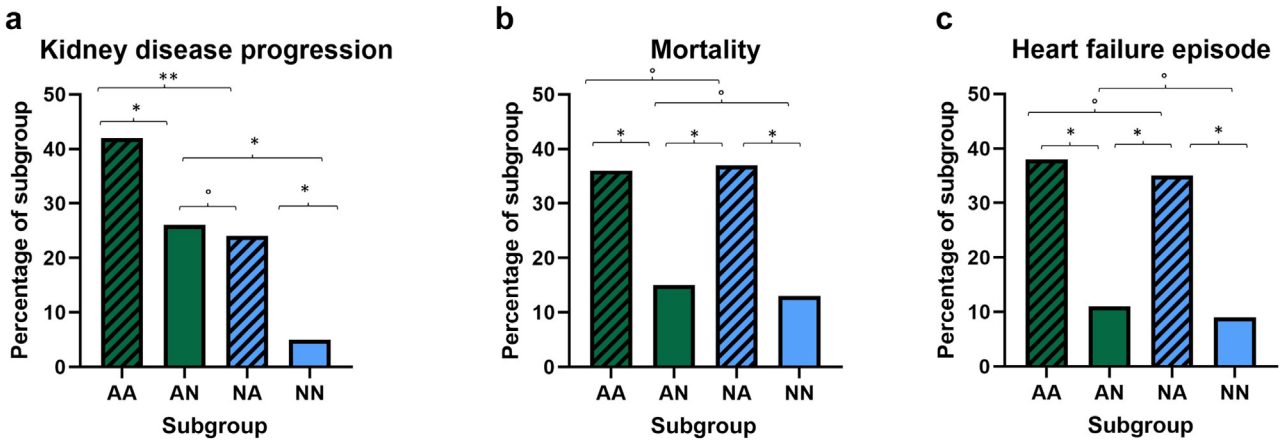


Figure 4 | Bar charts showing percentage of individuals in subgroups according to index acute kidney injury (AKI) exposure and AKI exposure during the follow-up period, who have (a) kidney disease progression, (b) mortality, and (c) heart failure episode, at 5 years. Missing data censored. *$P < 0.001$, **$P < 0.01$, °$P > 0.05$. AA, acute kidney injury in the index period and acute kidney injury during the follow-up period ($n = 138$); AN, acute kidney injury in the index period and no acute kidney injury during the follow-up period ($n = 268$); NA, no acute kidney injury in the index period and acute kidney injury during the follow-up period ($n = 67$); NN, no acute kidney injury in the index period and no acute kidney injury during the follow-up period ($n = 352$).

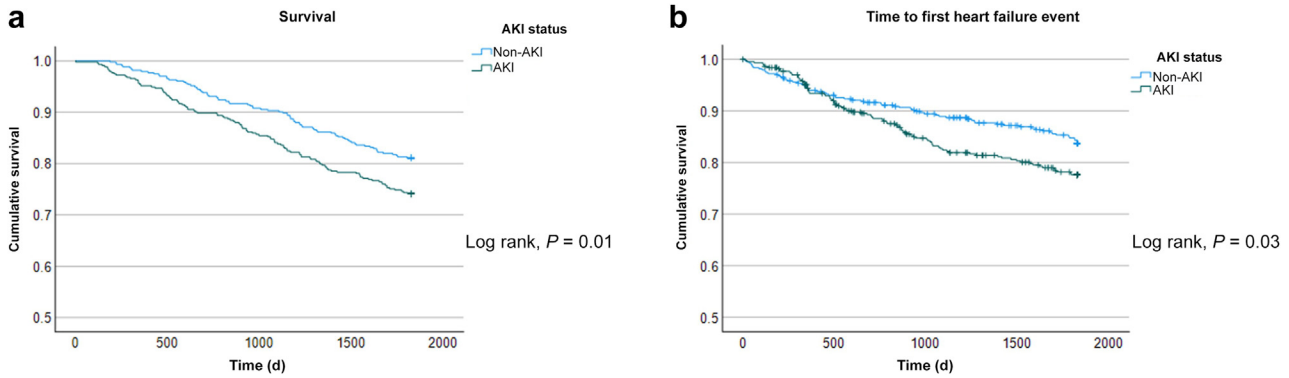


Figure 5 | Kaplan-Meier curves for outcomes of (a) mortality and (b) episodes of heart failure, comparing exposed and non-exposed groups. AKI, acute kidney injury.

However, the challenges of doing so are not insignificant, in terms of large numbers of affected patients and practical aspects of case finding and arranging follow-up across all clinical areas. Improved approaches to stratifying individual risk on the basis of clinical features (including eGFR and urine ACR) and novel biomarkers may offer potential solutions.[10,14,15]

The pattern of kidney disease progression we have reported suggests that nonrecovery from damage at the time of AKI is more important than later CKD progression. The protocolized follow-up period showed that kidney disease progression was characterized by failed recovery at 3 months in the majority of cases in the AKI group. This is supported by a previous retrospective study including patients without preexisting kidney disease that showed separation by 3 months in the proportion who developed CKD between AKI and control groups.[16] These findings are also consistent with animal models of AKI that show maladaptive repair mechanisms that lead to chronic damage, including proximal tubule damage, cell de-differentiation, and inflammatory and fibrotic signaling processes, follow immediately after the AKI episode.[17] This is clinically relevant, as it means that the focus for improving long-term outcomes should be on the early post-AKI period, although outstanding questions persist around the time course of changes between the time of AKI and day 90.

Only a small number of individuals in our cohort developed advanced CKD or kidney failure during the 5-year follow-up period, and the average time to reach this was almost 2 years. Numbers are small, so findings should be interpreted with caution, but the combination of preexisting advanced CKD (8 of 9 who started dialysis had baseline eGFR $<$ 45 ml/min per 1.73 m^2) plus an episode of AKI (6 of 9 who started dialysis were in the exposed group) appeared to be relevant and consistent with previous studies.[18] More importantly, our results suggest that in this setting, kidney failure is a rare outcome, so that the greater impact of AKI on population health in a general ward setting is seen via onset or progression of CKD and relationships with cardiovascular health.

We observed independent associations of AKI with mortality and heart failure events over the 5-year follow-up period. However, the critical role of nonrecovery of kidney function after AKI was shown in analyses where the association between these events and AKI disappeared when adjusting for markers of nonrecovery (3-month eGFR and urine ACR). A similar observation was seen in the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury Study.[5] It is therefore interesting to speculate whether the risk of mortality and heart failure after AKI arises via the development of CKD and its attendant risks on cardiovascular events or whether those with nonrecovery of AKI are also those who were more severely affected by the AKI episode or those who had preexisting risk factors. If the former, then this would further reinforce the importance of recovery of kidney function after an episode of AKI as a patient-centric outcome and target for future interventions.

The strengths of our study are that it is prospective, with a large sample size. The 2 cohorts were well matched, and few individuals were lost to follow-up. Baseline (preadmission) creatinine was available in all participants, and all AKI episodes

Table 7 | HR for the effect of AKI on mortality and heart failure episodes

Model	HR for the effect of AKI on mortality (95% CI)	*P*	HR for the effect of AKI on heart failure episodes (95% CI)	*P*
Unadjusted	1.44 (1.09–1.92)	0.01	1.38 (1.01–1.89)	0.05
Adjusted for age, Charlson index score, and diuretic at discharge	1.40 (1.05–1.86)	0.02	1.54 (1.01–2.20)	0.02
Adjusted for age, Charlson index score, diuretic at discharge, 3-mo delta eGFR, and 3-mo albuminuria	1.14 (0.84–1.56)	0.4	1.17 (0.83–1.65)	0.4

AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
HRs for AKI for 5-year mortality and heart failure episodes, shown unadjusted and adjusted using Cox proportional hazards analysis.

were adjudicated by a member of the study team. Limitations include that pre-AKI albuminuria results were not available. Its single-center design may limit generalizabilty of results, but the cohort description argues for its representativeness. In addition, the Fine-Gray subdistribution hazards model is limited by the timing of blood tests, which means that outcomes can occur only at 4 specified time points.

In conclusion, kidney disease progression after 5 years was common and strongly associated with AKI in a general hospitalized population with predominantly AKI stage 1. The pattern of kidney disease progression and associations with mortality and heart failure suggest that the effect of AKI on long-term outcomes is predominantly determined within the first 3 months and that nonrecovery of renal function is an important factor in this. Recurrent AKI is common in AKI survivors and is also associated with poor outcomes. Future strategies to improve outcomes could include interventions targeting better renal recovery from AKI and to improve postdischarge management so that a higher proportion of patients, as a minimum, receive a 3-month measurement of eGFR and urine ACR.

DISCLOSURE

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DATA STATEMENT

Due to existing data sharing permissions, summary statistics are available on request to the authors.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Figure S1. Cumulative incidence function calculated using the Fine-Gray model.

Supplementary Figure S2. Kaplan-Meier survival plot showing time to first cardiovascular event, comparing exposed and nonexposed groups.

Supplementary Table S1. Univariate associations with kidney disease progression at 5 year in the whole cohort.

Supplementary Table S2. Univariate association of acute kidney injury (AKI) duration with 5-year outcome.

Supplementary Table S3. Baseline characteristics of the groups matched using propensity score matching.

Supplementary Table S4. Multivariable analysis examining associations with kidney disease progression at 5 years after propensity score matching.

Supplementary Table S5. Analysis of estimated glomerular filtration rate (eGFR) slope as a sensitivity analysis for the effect of acute kidney injury (AKI) on subsequent eGFR.

Supplementary Table S6. Characteristics of individuals reaching the combined renal end point and those starting kidney replacement therapy.

Supplementary Table S7. Number of individuals in the exposed and nonexposed groups who developed at least 1 acute kidney injury (AKI) during the corresponding follow-up period.

Supplementary Table S8. Independent associations with total cardiovascular events examined using Cox regression analysis.

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