A comprehensive description of kidney disease progression after Acute Kidney Injury: results of a prospective, parallel group cohort study

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Abstract

Acute kidney injury (AKI) is associated with adverse long-term outcomes, but many studies are retrospective, focussed on specific patient groups or lack adequate comparators.

The ARID (AKI Risk in Derby) Study is a 5-year prospective parallel-group cohort study. Hospitalised cohorts with and without exposure to AKI were matched 1:1 for age, baseline renal function and diabetes. Estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (uACR) were measured at 3-months, 1, 3 and 5-years. Outcomes included kidney disease progression, heart failure episodes and mortality.

In 866 matched individuals, kidney disease progression at 5-years occurred in 94 (30%) of the exposed group versus 24 (7%) of those non-exposed (adjusted odds ratio (OR) 2.49 [95%CI 1.43 to 4.36]; *P*=0.001). In the AKI group, this was largely characterised by incomplete recovery of kidney function by 3-months. Further episodes of AKI during follow-up were more common in the exposed group (OR 2.71 [95% CI 1.94 to 3.77]; *P*<0.001) 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 3-month eGFR and uACR.

In a general hospitalised population, kidney disease progression after 5-years was common and strongly associated with AKI. The time-course of changes and the attenuation of associations with adverse outcomes after adjustment for 3-month eGFR

and uACR suggest that non-recovery of kidney function is an important assessment in post-AKI care and a potential future target for intervention.

Study registration: ISRCTN25405995

Keywords

Acute kidney injury, chronic kidney disease, long term outcomes, clinical nephrology

Introduction

Acute kidney injury (AKI) is common and increasing among hospitalised 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 standardised timed follow up assessments prevents clear descriptions of the patterns of changes in renal function after AKI and the mechanisms by which these may occur [3].

More recently the ASSESS-AKI study confirmed this increased risk of CKD following AKI in a large prospective US study [4]. The study population comprised patients from four 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 AKI 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 ASSESS-AKI study designs, but key differences in ARID 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 following AKI. Between May 2013 and May 2016, the study recruited two cohorts of people hospitalised at the Royal Derby Hospital, UK, who had survived to at least 90 days after hospital admission. One cohort consisted of people who had sustained 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/1.73m^2, eGFR stages 3A, 3B or 4), age (±5 years) and presence of diabetes. Approvals for the study were obtained from 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 old, had at least one in-patient serum creatinine measurement and a baseline creatinine within the preceding twelve 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 (KDIGO) criteria [8]. The baseline creatinine value was taken as the most recent stable serum creatinine prior to hospital admission. Urine output was not used to define AKI due to its inaccurate recording in a general hospitalised population. Other exclusion criteria were total or partial nephrectomy during index admission, pre-existing CKD stage G5 or receiving palliative care.

All AKI episodes were adjudicated by a member of the research team to confirm presence of AKI, KDIGO stage and duration (in days). Aetiology of AKI was determined by manual review of electronic patient records. 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 CKD Epidemiology Collaboration Equation) and albuminuria were measured at three months, one, three and five years after the index blood test. For the exposed group this was day of AKI onset and for the non-exposed group this was the first blood test in 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 seven hours in the central hospital laboratory. In addition to absolute eGFR values, the annualised eGFR trajectory (ml/min/1.73m^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 endpoints were compared between exposed and non-exposed groups: kidney disease progression, mortality, and heart failure episodes. Maximum follow-up for all outcomes was five years. Kidney disease progression was defined as decrease in eGFR of ≥25% associated with a decline in eGFR stage [9,10]. This definition

was used both in individuals with known CKD at baseline and those with baseline eGFR >60 ml/min/1.73m^2. A composite renal endpoint of doubling of serum creatinine, commencement of kidney replacement therapy (KRT) or eGFR <15 ml/min/1.73m^2 was also recorded. Individuals who had progressed to the composite renal end-point were also classed as having shown kidney disease progression. Albuminuria was defined as urine albumin creatinine ratio (uACR) ≥ 3.0 mg/mmol. Cross referencing with the local renal database was used to track 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 conducted using the statistical software SPSS version 25.0 (IBM Corporation, Chicago, IL) and SAS OnDemand for Academics. Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]), while categorical variables are presented as percentages. Paired t-test and Wilcoxon test were used for intragroup comparisons in the case of continuous variables. Student t-test and Mann-Whitney U test were used for intergroup comparisons for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. Kaplan-Meier survival curves and Cox regression analysis were used to examine mortality and heart failure episodes. Multivariable modelling was conducted to identify independent predictors of kidney disease progression. Each potential predictor variable was analysed independently to identify those with significant association (cut off P=0.25 so that all potentially important variables were included in the modelling), and then successive binary logistic regression performed with the most insignificant variables removed stepwise until only statistically significant

variables remained (P<0.05) based on P-values, pseudo-R-squared values and model prediction strength. Model assumptions were checked using the Box-Tidwell test. A competing risks analysis was performed using the Fine-Gray sub-distribution hazards model [11] to calculate the cumulative incidence function, accounting for competing risk of death and significant co-variables. Individuals were classed as having kidney disease progression at the earliest time point this was evident.

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 is shown in Figure 1. At five 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 detailed in Table 1. Matching was very good with few differences between the exposed and non-exposed groups. In particular, the proportion of participants with diabetes, pre-existing CKD, and who were ex- or current smokers were the same between groups. A greater proportion of participants in the exposed group were taking renin-angiotensin-aldosterone system inhibitors and non-steroidal anti-inflammatory agents at time of hospital admission.

Hospital stay data for each group are shown in Table 2. The exposed group had a longer hospital stay and more frequent rates of admission to the intensive care unit during the index admission, although the latter was uncommon (3.3% across whole group). AKI was most commonly stage 1 (59% of 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 compared to the non-exposed group (three months: 17% vs 3%; one year: 24% vs 4%; three years: 27% vs 7%; and five years: 30% vs 7%; $P<0.001$ for all comparisons between groups). This association was seen both in participants with known pre-existing CKD at baseline (44% vs 12%, $P<0.001$)

and those with baseline eGFR >60ml/min/1.73m^2 (24% vs 5%, *P*<0.001). 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 five years and associated adjusted odds ratios from binary logistic regression analyses. A full list of univariable associations with kidney disease progression are presented in Supplementary table S2. In the multivariable model AKI, diabetes, sex, Charlson index, change in eGFR from baseline to three months (delta eGFR) and albuminuria at three months were independent predictors of 5-year kidney disease progression. AKI was associated with kidney disease progression at five years in unadjusted model (OR 5.65 [95%CI 3.49 to 9.13]; *P*<0.0001) and remained so in the adjusted model (OR 2.49 [95%CI 1.43 to 4.36]; *P*=0.001]).

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 shown in Supplementary Tables S3 and S4.

We also conducted further analysis to account for the competing risk of death on the incidence of kidney disease progression. The cumulative incidence function calculated by the Fine-Gray sub-distribution 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 and age (Table 5). Details of the cumulative incidence function model are included in Supplementary Figure S1.

Thirdly, 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 the non-exposed group (Supplementary Table S5).

Development of advanced CKD

The numbers reaching the combined renal endpoint (doubling of serum creatinine, eGFR <15 ml/min/1.73m^2 or KRT) within five years were low, although significantly greater in the exposed group (20 [5%] vs 6 [1%]; *P*=0.005). Of those reaching the combined renal endpoint, nine commenced KRT for end-stage kidney disease, of whom six were in the exposed group. The median time from index hospitalisation to start of KRT was 634 days (IQR 313 to 1247 days). Whilst the numbers are small, the most ostensible feature in those who reached the combined renal endpoint was worse baseline renal function. In the nine that commenced KRT, mean baseline eGFR was 28 ± 11ml/min/1.73m^2 and all had pre-existing CKD (five had CKD stage G4, three CKD stage G3B and one CKD stage G3A). Further details are included in Supplementary table S1.

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 summarised in Figure 3. Between baseline and three months, the annualised eGFR trajectory was -20.5 ± 44.3ml/min/1.73m^2 per year in

the exposed group, while there was an apparent increase in eGFR of +9.9 ± 40.2ml/min/1.73m^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 two groups from three months to one year, one to three years, and three to five years.

Albuminuria and effect on CKD classification

Albuminuria (ACR ≥3mg/mmol) was more common in the exposed group at each time point. At three months, 180 (42%) of the exposed group had albuminuria compared with 100 (23%) of the non-exposed group (P<0.001). The distribution according to albuminuria category is shown in Table 6.

At 5 years, 90 (29%) of those 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 progressed to kidney failure). Comparative numbers in the non-exposed group were 65 (19%) with albuminuria, 234 (67%) without albuminuria and 49 (14%) had 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 KDIGO CKD criteria to the cohort led to more individuals meeting the criteria for CKD diagnosis. 157 (51%) individuals in the exposed group and 95 (27%) in the non-exposed group met eGFR only criteria (eGFR<60) at 5 years. The number categorised 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 (34%) of participants had at least one further episode of AKI during follow-up versus 67 (16%) in the non-exposed group (OR 2.71 [95% CI 1.94 to 3.77]; *P*<0.001). The period of follow-up in which AKI episodes occurred is shown in Supplementary table S6. Independent associations with 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 highest in those who had AKI in both the index admission and also during follow-up. Proportions with kidney disease progression were similar between the exposed group without AKI during follow-up and control group who did have AKI during follow-up, with significantly lower numbers in those who never had AKI. These data are shown in Figure 4. Additionally, 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 index admission, 3m albuminuria and Charlson index score (adjusted OR 1.849 [1.350-2.530, *P*<0.001).

Mortality

Over the 5-year follow-up period, mortality was higher in the exposed group (26%) compared with 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).

Incidence of heart failure.

In the exposed group, 90 (21%) had at least one episode of heart failure requiring hospitalisation compared with 67 (16%) of 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 the non-exposed group, (1589 ± 24 days in the exposed group compared with 1657 ± 22 days in the non-exposed group, Log rank 4.87 *P*=0.027, 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 eGFR at 3 months or recurrent AKI (Table 7). Similar patterns were seen with total cardiovascular events (supplementary Figure S2, Table S7).

Discussion

We have demonstrated increased incidence of kidney disease progression, recurrent AKI, heart failure admissions and mortality following 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. Non-recovery of kidney function and albuminuria at three months, as well as subsequent episodes of AKI, appear to be important determinants of subsequent heart failure and mortality.

It is well-recognised 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 included studies comprising 96.5% of pooled patients), 50% were from ICU or cardiac surgery settings, and none incorporated albuminuria in their definition of CKD [3,13]. Prospective studies with lower risk of residual confounding and with protocolised 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 renal function and those with pre-existing CKD. The strength of this association was shown in multivariable and competing risks analyses. Additionally, there was an additive effect of multiple AKI

episodes on 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 ASSESS-AKI, which reported similar magnitudes of increased adjusted hazard ratios of CKD incidence (3.98) and CKD progression (2.37) following 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 ARID reflects AKI in a general ward-based setting, in which 60% of cases were AKI stage 1, our results emphasise the importance of post-discharge AKI care in which measuring eGFR and urinary ACR at 3-months provides important information of future risk. 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 based on clinical features (including eGFR and uACR) and novel biomarkers may offer potential solutions [10,14,15]

The pattern of kidney disease progression we have reported suggests that non-recovery from damage sustained at the time of AKI is more important than later CKD progression. The protocolised follow-up showed that kidney disease progression was characterised 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 pre-existing kidney disease that showed separation by 3-months in the proportion that 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 signalling processes, follow immediately from 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 end-stage kidney disease during the five-year follow up period, and the average time to reach this was almost two years. Numbers are small so findings should be interpreted with caution, but the combination of pre-existing advanced CKD (eight from nine who started dialysis had baseline eGFR <45ml/min) plus an episode of AKI (six from nine who started dialysis were in the exposed group) appeared to be relevant and consistent with previous studies [18]. More importantly, our results suggest in this setting, kidney failure is a rare outcome, so that the greater impact on population health from AKI 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 five-year follow-up period. However, the critical role of non-recovery of kidney function after AKI was shown in analyses where the association between these events and AKI disappeared when adjusting for markers of non-recovery (3-month eGFR and uACR). A similar observation was seen in ASSESS-AKI [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 non-recovery of AKI are also those who were more severely affected by the

AKI episode, or who had pre-existing risk factors. If the former, then this would further reinforce the importance of recovery of renal function after an episode of AKI on patient-centric outcomes as a target for future interventions.

The strengths of our study are that it is prospective with a large sample size. The two cohorts were very well matched, and few individuals were lost to follow-up. Baseline (pre-admission) creatinine was available in all participants and all AKI episodes were adjudicated by a member of the study team. Limitations include that pre-AKI albuminuria results were not available. Its single centre design may limit generalisabilty 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 mean that outcome can only occur at four specified time points.

In conclusion, kidney disease progression after 5 years was common and strongly associated with AKI in a general hospitalised 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 non-recovery 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 post-discharge management so that a greater proportion of patients, as a minimum, receive a three-month measurement of eGFR and uACR.

Disclosure Statement

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Tables and figures

Figure legends

Figure 1. Consort diagram showing participants through ARID study.

Figure 2. Mean eGFR (ml/min/1.73m^2) at different time points in the study comparing exposed and non-exposed groups.

Mean eGFR at: baseline 69.6 ± 20.4 (AKI) vs 70.4 ± 20.3 (non-AKI) ml/min/1.73m^2; lowest in stay 30.1 ± 12.4 vs 68.1 ±21.2 ml/min/1.73m^2; last in stay 59.2 ±24.7 vs 76.2 ±21.3 ml/min/1.73m^2; three months, 63.2 ± 21.6 vs. 73.1 ± 20.4 ml/min/1.73m^2; one year, 60.5 ± 20.4 vs. 71.3 ± 20 ml/min/1.73m^2; three years, 60.6 ± 20.1 vs. 69.6 ± 20.3 ml/min/1.73m^2; and five years, 62.4 ± 27.7 vs. 73 ± 29 ml/min/1.73m^2; P= 0.6 for comparison at baseline, P<0.0001 for all other comparisons between groups.

Figure 3. Annualised eGFR (ml/min/1.73m^2/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≥0.1

Within group differences between time periods were significant for comparisons with baseline to 3-month periods versus later time periods (P<0.0001 for all comparisons in both groups), and 3-month to 1-year period vs. 1-year to 3-year period only in the AKI group (P=0.02). No significant differences were observed in either group comparing 1-year to 3-year period vs. 3-year to 5-year period (P=0.7 for exposed and P=0.6 for non-exposed groups).

Figure 4. Bar charts showing percentage of individuals in subgroups according to index AKI exposure and follow-up period AKI exposure, who have (a) kidney disease progression (b) mortality (c) heart failure episode, at 5 years. Missing data censored. AA, AKI index period and AKI during follow up (n=138); AN, AKI in index period and non-AKI in follow up period (n=268); NA, non-AKI in index period and AKI during follow up period (n=67); NN, non-AKI in index period and non-AKI during follow up period (n=352).

* P<0.001, ** P<0.01, ° P>0.05

Figure 5. Kaplan-Meier curves for outcomes of (a) mortality and (b) episodes of heart failure comparing exposed and non-exposed groups.

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-value**
Age (years)	69.6 ± 10.1	69.7 ± 9.8	
Male sex [n (%)]	248 (57)	221 (51)	0.07
White ethnicity [n (%)]	412 (95)	397 (92)	0.1
Smoking status [n (%)]			0.1
Never	160 (41)	166 (42)	
Ex	194 (50)	211 (53)	
Current	35 (9)	21 (5)	
Charlson index score	1 [0-2]	0 [0-2]	0.001
Baseline eGFR (ml/min/1.73m^2)	69.6 ± 20	70.3 ± 20	
Baseline eGFR stage [n (%)]			
>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 [n (%)]	94 (22)	94 (22)	
Ischaemic heart disease [n (%)]	44 (10)	42 (10)	0.8
Cerebrovascular disease [n (%)]	4 (1)	4 (1)	1.0
Peripheral vascular disease [n (%)]	15 (4)	11 (3)	0.4
Heart failure [n (%)]	35 (8)	25 (6)	0.2
Liver disease [n (%)]	3 (1)	1 (0.2)	0.3
Chronic lung disease [n (%)]	65 (15)	81 (19)	0.2
Cancer [n (%)]	27 (6)	23 (5)	0.6

Data are expressed as mean ± standard deviation, median[IQR] or percentages, as appropriate.
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.
*Exposed vs. non-exposed.

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

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

Data are expressed as mean ± standard deviation, median [IQR] or percentages, as appropriate.
AKI, acute kidney injury; AKD, acute kidney disease; ICU, Intensive Care Unit; KRT, kidney replacement therapy; NSAID, non-steroidal anti-inflammatory drug; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
*Exposed vs. non-exposed.

Table 3. Factors associated with kidney disease progression at 5 years using binary logistic regression.

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

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

Variable	Subdistribution hazard ratio (95%CI)	Significance
AKI	2.633 (1.767-3.846)	*P*<0.001
Albuminuria at 3-months	1.729 (1.232-2.426)	*P*=0.002
Age	1.035 (1.016-1.056)	*P*<0.001
Charlson score	1.155 (1.053-1.268)	*P*=0.002
Change in eGFR baseline to 3 months	0.941 (0.924-0.958)	*P*<0.001

[a] The sub distribution hazard ratio for the Fine-Gray model demonstrates the direct impact of the variable on the cumulative incidence function. A value over 1 is interpreted as increasing the risk of experiencing the outcome, and if greater than a different variable, has a more significant impact than that variable. However, the magnitude of impact is unknown.

Table 5. Albuminuria levels measured three months after index hospitalisation [b].

3-month albuminuria measurement	Exposed group n=432	Non-exposed group n=429	significance
ACR<3 mg/mmol	252 (58%)	330 (77%)	*P*<0.001
ACR 3-30 mg/mmol	129 (30%)	81 (19%)	*P*<0.001
ACR >30-300 mg/mmol	51 (12%)	18 (4%)	*P*<0.001
Median ACR at 3 months (mg/mmol)	1.8 [0.6-9.4]	0.8 [0.1 to 2.8]	*P*<0.001

[b] Only participants with proteinuria data available included in total numbers.

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

Variable	*Unadjusted odds ratio [CI]*	*Significance*	*Adjusted Odds ratio [CI]*	*Significance*
AKI during index admission	2.705 [1.940-3.772]	*P*<0.001	2.146 [1.467 – 3.140]	*P*<0.001
Baseline eGFR	0.975 [0.967-0.983]	*P*<0.001	0.980 [0.970-0.989]	*P*<0.001
Current or past smoker	1.470 [1.043-2.074]	*P*=0.03	1.614 [1.106 – 2.356]	*P*=0.01
Hb at 3 months	0.975 [0.965-0.985]	*P*<0.001	0.983 [0.972-0.995]	*P*=0.004
Albuminuria at 3 months	3.157 [2.273-4.386]	*P*<0.001	2.060 [1.409-3.012]	*P*<0.001

Table 7. Hazard ratio of AKI on mortality and episodes of heart failure.

Hazard ratios for AKI for 5-year mortality and heart failure episodes, shown unadjusted and adjusted using Cox proportional hazards analysis.

Model	Hazard ratio for effect of AKI on mortality	Significance
Unadjusted	1.44 [1.09-1.92]	*P*=0.01
Adjusted for statistically significant variables (age, Charlson score, diuretic at discharge)	1.40 [1.05-1.86]	*P*=0.02
Adjusted for age, Charlson score, diuretic at discharge, 3m delta eGFR and 3m albuminuria	1.14 [0.84-1.56]	*P*=0.4

Model	Hazard ratio for effect of AKI on heart failure episodes	Significance
Unadjusted	1.38 [1.01-1.89]	*P*=0.05
Adjusted for statistically significant variables (age, Charlson score, diuretic at discharge)	1.54 [1.01-2.20]	*P*=0.02
Adjusted for age, Charlson score, diuretic at discharge, 3m delta eGFR and 3m albuminuria	1.17 [0.83-1.65]	*P*=0.4