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ORIGINAL ARTICLE

Effect of multiple episodes of acute kidney injury on mortality: an observational study

Heather Walker [1,2], Nicosha De Souza[2], Simona Hapca[2,3], Miles D. Witham[4] and Samira Bell [1,2]

[1]Renal Unit, Ninewells Hospital, Dundee, UK, [2]Population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK, [3]Division of Computing Science and Mathematics, University of Stirling, Stirling, UK and [4]AGE Research Group, NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust, Newcastle University, Newcastle, UK

Correspondence to: Heather Walker; E-mail: hwalker7@nhs.net; Twitter handle: @SamiraBell76

ABSTRACT

Background. Patients who survive an episode of acute kidney injury (AKI) are more likely to have further episodes of AKI. AKI is associated with increased mortality, with a further increase with recurrent episodes. It is not clear whether this is due to AKI or as a result of other patient characteristics. The aim of this study was to establish whether recurrence of AKI is an independent risk factor for mortality or if excess mortality is explained by other factors.

Methods. This observational cohort study included adult people from the Tayside region of Scotland, with an episode of AKI between 1 January 2009 and 31 December 2009. AKI was defined using the creatinine-based Kidney Disease: Improving Global Outcomes definition. Associations between recurrent AKI and mortality were examined using a Cox proportional hazards model.

Results. Survival was worse in the group identified to have recurrent AKI compared with those with a single episode of AKI [hazard ratio = 1.49, 95% confidence interval (CI) 1.37–1.63; $P < 0.001$]. After adjustment for comorbidities, stage of reference AKI, sex, age, medicines that predispose to renal impairment or, in the 3 months prior to the reference AKI, deprivation and baseline estimated glomerular filtration rate (eGFR), recurrent AKI was independently associated with an increase in mortality (hazard ratio = 1.25, 95% CI 1.14–1.37; $P < 0.001$). Increasing stage of reference AKI, age, deprivation, baseline eGFR, male sex, previous myocardial infarction, cerebrovascular disease and diuretic use were all associated with an increased risk of mortality in patients with recurrent AKI.

Conclusions. Recurrent AKI is associated with increased mortality. After adjusting for patient characteristics, the increase in mortality is independently associated with recurrent AKI and is not solely explained by other risk factors.

Keywords: acute kidney injury, mortality, recurrent acute kidney injury, risk factors, survival

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INTRODUCTION

Acute kidney injury (AKI) is associated with increased risk of mortality and is predictive of poor prognosis in hospitalized patients [1, 2]. AKI is also a risk factor for future cardiovascular disease and progression of chronic kidney disease (CKD) [1]. Longer duration of AKI is associated with worse outcomes compared with those with rapid and sustained reversal to baseline renal function [3]. Previous work has shown that around 30% of the patients with AKI who survive initial hospitalization develop a repeated or recurrent episode of AKI [4] and that up to one-third of older people who were hospitalized with AKI were re-hospitalized in the following 12 months with a recurrent AKI [5].

Episodes of AKI have been shown to have a cumulative effect in increasing the risk of progression to CKD [5–8], and recurrent AKI is associated with increased future mortality in comparison with individuals who have a single episode of AKI [4, 5, 7, 9]. The pathogenesis of this is not clearly understood in humans but may be related to uraemia, the activation of inflammation and fibrosis, and resultant microvascular and endothelial damage that drives progressive renal damage, dysfunction and future cardiovascular disease [10, 11]. Other studies have attempted to define the risk factors in the cohort of patients that go on to develop recurrent AKI [4, 5, 7, 12]. These data are, however, limited with only a small number of studies focusing on recurrent AKI and the impact that further episodes of AKI have after recovery following an initial episode of AKI, with some inconsistent findings. Studies to date have also focused only on hospital-based AKI [4, 6–9, 11, 13].

There is a lack of clarity around the association between AKI and its concomitant adverse outcomes, including mortality. At present, it is unclear if these adverse outcomes are driven by AKI, progression to CKD and/or the associated sequelae, or if AKI is a marker of other comorbidities and patient frailty.

The aims of this study are to assess whether recurrence of AKI is an independent risk factor for mortality or if excess mortality is explained by other factors.

MATERIALS AND METHODS

Study design and setting

Population-level healthcare datasets from the Tayside region of National Health Service (NHS) Scotland, UK, were used to retrospectively identify all residents in Tayside aged ≥18 years with biochemical evidence of an episode of AKI between 1 January and 31 December 2009 (index AKI).

A 6-year period from 1 January 2003 to 31 December 2008 was used to identify patients who had previous biochemical evidence of AKI (recurrent AKI). Patients were followed up until time of death or 11 January 2019, whichever was sooner. Time to death or end of follow-up was then calculated from the date of peak creatinine of the index AKI event.

There was no evaluation of AKI or progression to CKD following the index AKI.

Ethical approval

Data provision and linkage were carried by the University of Dundee Health Informatics Centre (HIC) [14], with analysis of anonymized data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service.

AKI definition

AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine-based criteria [15], and AKI identification was conducted using the NHS England AKI algorithm (Supplementary Data, Figure S1). AKI stage was classified according to the highest stage of AKI during the AKI episode. Incident or unique AKI events were defined as an AKI for the same patient that was >7 days apart. All patients with missing creatinine measurements in 2008, which meant it was not possible to calculate a baseline creatinine, and those who received chronic renal replacement therapy (RRT) during the 2003–15 time period were excluded from the study.

Data sources

Data were linked between the following datasets: Scottish Renal Registry, Community Health Index (CHI) register, Scottish Morbidity Record of hospital admissions (SMR01), laboratory results database, medicines dispensed by community pharmacies, General Register Office death database and Scottish Care Information–Diabetes Collaboration [16].

Patient demographic characteristics including age at reference AKI, sex and social deprivation based on the Scottish Index of Multiple Deprivation (SIMD) [17] were obtained from the CHI register.

The SMR01 data provided information on admission and discharge dates as well as discharge diagnosis (based on International Classification of Diseases 10th revision codes). Discharge diagnosis from all admissions prior to the reference AKI was used to assess each participant's comorbidities and calculate the Charlson Comorbidity Index score [18, 19] for case-mix adjustment.

The Modification of Diet in Renal Disease study equation [20] was used to calculate baseline estimated glomerular filtration rate (eGFR) using the median creatinine in the previous 8–365 days or lowest creatinine value in the previous 7 days; if both were available median creatinine in the previous 8–365 days was used. Creatinine assays were traceable to isotope dilution mass spectrometry.

Exposure to medicines that predispose to renal impairment or hypotension [non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists (ARB), diuretics, β-blockers] in 3 months prior to the reference AKI was ascertained from dispensed community prescribing data.

The laboratory database was used to calculate baseline renal function and episodes of AKI as described above. The median creatinine was calculated if there was more than one serum creatinine measurement taken on the same day.

Statistical analysis

Baseline characteristics were summarized using means and standard deviations (SDs) for normally distributed continuous data or medians and interquartile ranges for skewed data. Categorical variables were summarized using frequencies and percentages. Comparison of baseline data for recurrent AKI versus first AKI were made using t-tests, Chi-squared tests and Mann–Whitney tests, as appropriate. Kaplan–Meier survival curves were used to estimate and compare survival function of patient with recurrent AKI versus first-time AKI at index and to calculate median survival time in the two groups. Cox proportional hazard models were used to examine the association between AKI status (whether recurrent AKI or first AKI) and

mortality. The effect size of the association was provided by the hazard ratio (HR) of recurrent AKI versus first AKI unadjusted or adjusted for patients' demographics characteristics, comorbidity and prior medication. Covariates included in the model were based on clinical expertise and previous evidence in this area. Several covariates included in the model violated the proportional hazards assumptions. However, when the model was run without these covariates, the effect of recurrent AKI remained similar. The covariates that violate the assumptions only contribute a small proportion of variance in the model and inclusion of all variables improved the fit of the model, tested using the Harrell's C statistic. Additionally, the Kaplan–Meier survival curves suggest that the hazards do not appear to vary over time.

Covariates included in the final model were age, sex, diabetes mellitus, AKI stage of reference AKI, derivation (using the SIMD deciles), previous myocardial infarction (MI), peripheral vascular disease, cerebrovascular disease and use of diuretics, ACEi or ARB, NSAIDs and β-blockers in the 3 months prior to the reference AKI.

Covariates were tested for collinearity, and no collinear variables were included in the final model.

All analyses were carried out in IBM SPSS (version 21) and STATA (version 14) software. A $P < 0.05$ was considered statistically significant.

Missing data

From the recurrent AKI group 7 patients and from the non-recurrent AKI group 51 patients had missing SIMD decile. These patients were included with missing SIMD data.

RESULTS

Participants

Figure 1 represents a flowchart of the patient cohort selection and exclusions. The study assessed 255 466 patients who had creatinine measurements taken between 2003 and 2009. A total of 721 patients were excluded as they were receiving RRT. A total of 116 630 patients were excluded as they had creatinine measurements only in 2009 and none in 2003–08. A total of 1667 patients with 13 634 creatinine measurements were excluded as they were <18 years old at the time of creatinine measurements. Among the 136 448 eligible patients, 1 167 329 creatinine measurements were taken over the time period 2003–09. A total of 7128 (5.2%) patients experienced an episode of AKI at any time in the study period.

In 2009, there were 3533 patients identified as having experienced an AKI, of which 880 (25%) had at least one prior AKI in the period 2003–08. The cumulative total in the 6-year time period prior to 2009 was 1740 AKI events. In total, 15 cases were reviewed where the time between the previous AKI and reference AKI was ≤14 days. This led to nine patients being excluded as eight were found to be unresolved AKI events and one case was progressive CKD. A total of 3524 patients with 5202 AKI events were included in the final analysis. The majority of these patients had a single episode of AKI, in 2009, with no evidence of previous AKI 2003–08, 2644 (75%). A total of 880 patients (25%) had prior AKI between 2003 and 2009.

Baseline characteristics

Table 1 describes patient characteristics and demographics for those with and without recurrent AKI.

In the majority of patients with recurrent AKI, 517 (58.8%) had one previous AKI episode detected between 2003 and 2008, 195 (22.2%) had two previous AKI episodes, 76 (8.6%) had three previous AKI episodes and 92 (10.4%) had more than four previous AKI episodes. The median time between the reference AKI and previous AKI episode in 2003–08 was 1.21 years (interquartile range (IQR) = 0.58–2.43 years).

Survival

A total of 2501/3524 (71.0%) patients died over a median (IQR) follow-up of 3.17 years (0.28–9.19 years). In the non-recurrent AKI group, 1776/2644 (67.2%) patients died over a median (IQR) follow-up of 3.86 years (0.33–9.28 years). For patients with recurrent AKI, 725/880 (82.4%) patients died over a median (IQR) follow-up time of 1.57 years (0.18–6.48 years). Figure 2 shows the Kaplan–Meier survival curves for the two groups. Overall survival was significantly shorter in the group identified to have recurrent AKI (HR = 1.49, 95% CI 1.37–1.63; $P < 0.001$). There was no difference in survival among people with recurrent AKI when comparing the different stages of prior AKI (Figure 3). There was also no difference in survival when comparing those that had experienced a more recent recurrent AKI (previous AKI within 365 days of index AKI) compared with those who had experienced a previous AKI less recently (previous AKI ≥365 days prior to index AKI) (Figure 4). The adjusted survival model presented in Table 2 showed that risk of mortality following recurrent AKI was significantly increased compared with first AKI (HR = 1.25, 95% CI 1.14–1.37; $P < 0.001$). In addition, increasing AKI stage at the reference AKI, male sex, increasing age, diuretic use, deprivation, baseline eGFR, and previous MI and cerebrovascular disease were all associated with increased risk of mortality (Table 2). Use of ACEi or ARB, NSAIDs and β-blockers in 3 months prior to AKI were all associated with decreased risk of mortality (HR = 0.72, 95% CI 0.66–0.78; $P < 0.001$, HR = 0.81, 95% CI 0.70–0.93; $P = 0.002$ and HR = 0.89, 95% CI 0.81–0.98; $P = 0.016$, respectively).

DISCUSSION

We found that patients with recurrent AKI had increased risk of death compared with those with a single episode of AKI. Recurrent AKI was an independent predictor of mortality after adjustment for confounders including age, sex, deprivation, comorbidities, underlying renal impairment and medicines that predispose to renal impairment or hypotension. Increasing stage of reference AKI, increasing age, deprivation, lower baseline eGFR, previous MI and cerebrovascular disease, male sex and diuretic use were all associated with an increased risk of mortality in patients with recurrent AKI.

Our findings showed that patients with a baseline eGFR 45–59 mL/min/1.73 m^2 and 30–44 mL/min/1.73 m^2 had increased risk of mortality compared with those with a baseline eGFR >60 mL/min/1.73 m^2; however, this relationship was not true in the groups with baseline eGFR 15–29 mL/min/1.73 m^2 and <15 mL/min/1.73 m^2. The results may be due to the smaller numbers in these groups, the fact that these groups are more likely to already be under nephrology care or that the underlying pathological processes that are driving increased mortality in recurrent AKI are already present as part of advancing CKD.

Studies in animal models have demonstrated that AKI results in permanent damage to the microvascular structure of the kidney and maladaptive repair mechanisms that result in inflammatory and fibrotic changes. This can lead to progressive

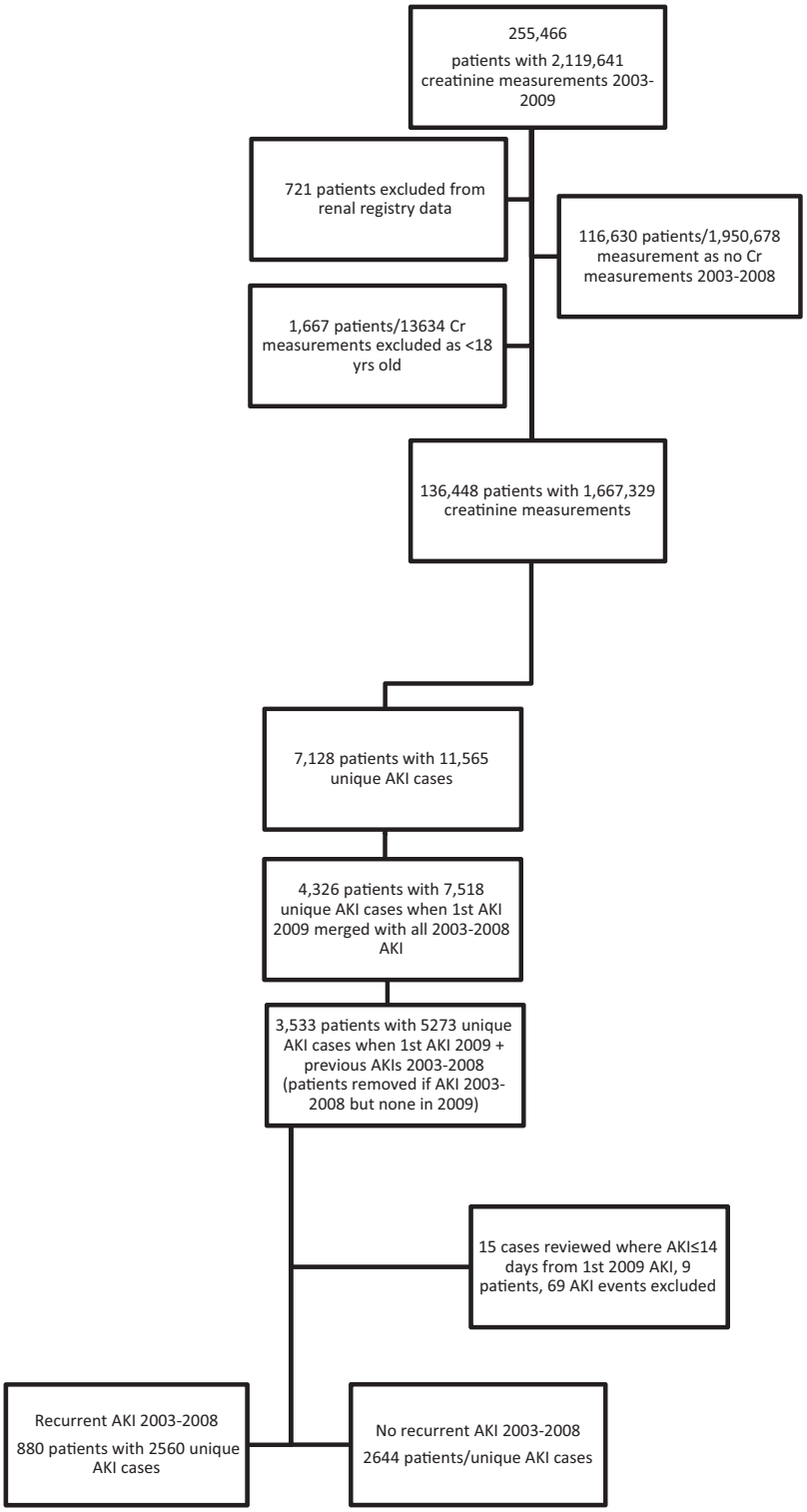

FIGURE 1: Summary of patient cohorts and exclusions.

structural and functional kidney damage and may potentiate the effects of recurrent injury [21, 22]. In a study of patients with diabetes mellitus and recurrent episodes of AKI, each episode of AKI was shown to have a cumulative increase in risk of future development of CKD, with each AKI episode doubling the risk of CKD [6]. This finding of increasing risk of CKD with recurrent AKI episodes has been replicated in cohorts including patients without diabetes mellitus [5, 7, 8]. In addition, recurrent AKI has also been shown to be associated with increased mortality compared with those with a single AKI episode [4, 5, 7, 9].

Studies have attempted to define risk factors for developing recurrent AKI. Harris *et al.* [7] did not find demographics (age, male sex, black ethnicity), baseline renal function, duration of AKI or comorbidities (CKD, hypertension, diabetes mellitus) to

Table 1. Baseline characteristics: recurrent AKI versus no evidence of recurrent AKI

Characteristic	Recurrent AKI 2003–08	No recurrent AKI 2003–08	P-value
Patients, *n*	880	2644	
Unique AKI cases, *n*	2558	2644	
Age, mean (SD), years	72.54 (15.6)	68.69 (18)	<0.001
Baseline SCr, median (IQR), μmol/L	91 (65–124)	74 (58–94)	<0.001
Sex, *n* (%)			
Female	479 (54.4)	1524 (57.6)	0.096
Male	401 (45.6)	1120 (42.4)	
AKI stage, *n* (%)			
1	634 (72)	1961 (74.2)	0.029
2	129 (14.7)	416 (15.7)	
3	117 (13.3)	269 (10.2)	
Source of requesting Cr from start of AKI, *n* (%)			
Hospital consultant	2067 (80.8)	2085 (78.9)	0.136
General practitioner	488 (19.1)	546 (20.7)	
Missing	3 (0.1)	13 (0.5)	
SIMD, *n* (%)	Some missing		
1–3 (most deprived)	231 (26.3)	649 (24.5)	0.691
4–7	355 (40.3)	1083 (41)	
8–10 (least deprived)	287 (32.6)	861 (32.6)	
Charlson Comorbidity Index, *n* (%)			
Low (0)	124 (14.1)	926 (35)	<0.001
Medium (1 or 2)	341 (38.8)	1095 (41.4)	
High (≥3)	415 (47.2)	623 (23.6)	
Baseline eGFR (from median creatinine previous 365 days), *n* (%), mL/min/1.73 m^2			
≥60	487 (55.3)	2069 (78.2)	<0.001
45–59	182 (20.7)	323 (12.2)	
30–44	139 (15.8)	196 (7.4)	
15–29	63 (7.2)	49 (1.9)	
<15	9 (1)	8 (0.3)	
Diabetes mellitus			
Type 1	26 (3)	43 (1.6)	<0.001
Type 2	277 (31.5)	557 (21)	
Diuretic	451 (51.2)	1085 (41)	<0.001
ACEi/ARB	346 (39.3)	1042 (39.4)	0.961
NSAID	69 (7.8)	308 (11.6)	0.002
β-blocker	290 (33)	664 (25.1)	<0.001
MI	157 (17.8)	328 (12.4)	<0.001
Peripheral vascular disease	15 (1.7)	13 (0.5)	<0.001
Cerebrovascular disease	204 (23.2)	361 (13.7)	<0.001

be associated with recurrent AKI. They showed only the presence of AKI at time of hospital admission to be associated with recurrent AKI. One proposed explanation for this is that patients with highest risk of developing recurrent AKI, such as those with multi-morbidity or severe illness, are more likely not to recover and therefore would not be exposed to the future risk of recurrence. However, more recent studies have shown different results. Rodriguez *et al.* [5] showed that Type 2 diabetes mellitus, ischaemic heart disease and higher serum creatinine at the time of first AKI were all independently associated with an increased risk of further episodes of AKI, and Siew *et al.* [9] showed that older age, lower baseline eGFR, lower serum albumin, congestive heart failure, advanced liver disease, dementia, diabetes mellitus and coronary artery disease were all associated with recurrent AKI. Most recently a large retrospective cohort study showed that 28.6% of their population who had previous AKI experienced recurrent AKI. They found that patients who experienced recurrent AKI were older and had more co-morbidities compared with those who had survived a single AKI, but did not go on to have recurrent AKI [4]. Our study supports these findings with 25% of patients experiencing recurrent AKI, and that this group was older with more co-morbidities.

Rodriguez *et al.* [5] showed that among the patients they examined with recurrent AKI episodes, 44% of them developed their second AKI episode during the first 6-month time period following initial discharge, with this number increasing further to 58% at 1 year. They demonstrated that cardiovascular events were more common in patients with recurrent AKI and found that when they followed patients up over 4 years following their first AKI, the most common cause of death was a cardiovascular event followed by malignancies and infections. They also demonstrated that mortality was higher in the group of patients who had a recurrent AKI in comparison with those with a single episode. Similarly, Siew *et al.* [9] showed that of the 25% of patient who developed recurrent AKI, 58% had occurred within the 90 days following discharge from the initial AKI and that patients who had developed recurrent AKI had a higher risk of death at 1 year compared with those who did not have recurrent AKI (35% versus 18%; $P < 0.001$). We have replicated this finding showing that patients who have evidence of recurrent AKI in

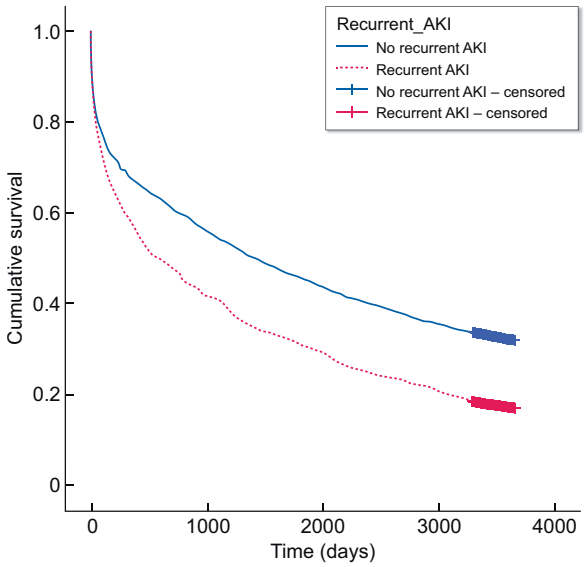

FIGURE 2: Kaplan–Meier plot of overall survival in patients with recurrent AKI compared with patients with no evidence of recurrent AKI.

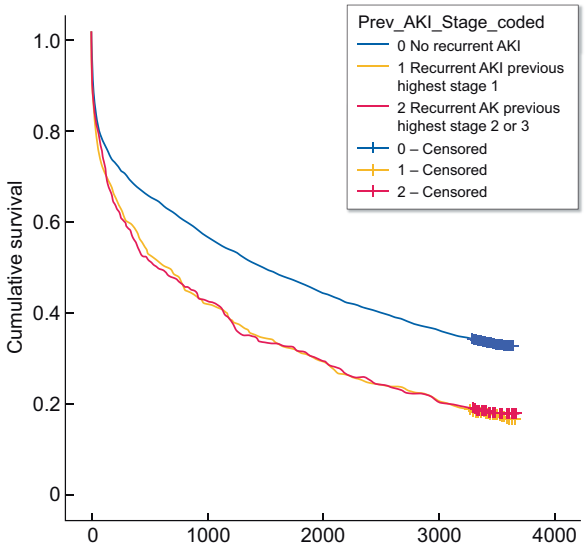

FIGURE 3: Kaplan–Meier plot of overall survival in patients with recurrent AKI Stage 2 or 3 compared with patients with recurrent AKI Stage 1 and patients with no evidence of recurrent AKI.

the previous 6-year period have higher future mortality than patients who have no previous evidence of AKI.

Preventing recurrent AKI may currently be an under-utilized mechanism of reducing the longer term implications such as cardiovascular disease and CKD. A previous study has shown that only a minority of patients that survive AKI are referred for nephrology follow-up [12]. The optimal care and follow-up after AKI remain to be established. Due to the relationship between AKI and cardiovascular disease, CKD and mortality, there is a need to define a high-risk population. This may then influence how patients with AKI are followed-up and has the possibility of reducing future morbidity and mortality. Our study aimed to identify risk factors that were associated with increased mortality following recurrent AKI. Our data show that patients who have experienced a recurrent AKI are less likely to be prescribed NSAIDs in the 3 months prior to the reference AKI. This may suggest that preventative measures such as avoiding prescribing nephrotoxic medications, including NSAIDs, to patients who previously have had an AKI to prevent future risk of AKI is being considered and employed. Therefore, this may represent a selection bias in our study. When adjusting for drugs used in the 3 months prior to AKI, ACEi/ARB, NSAIDs and β-blockers were all associated with a lower risk of mortality. Again, this may represent selection bias but it may also be that patients who are on these medications may get AKI for different reasons that might be associated with a lower risk of future mortality. For example, patients taking ACEi/ARB will be more susceptible to AKI if they become dehydrated and continue taking their medications, whereas individuals not on ACEi/ARB may require a more severe illness or 'hit' for them to develop AKI.

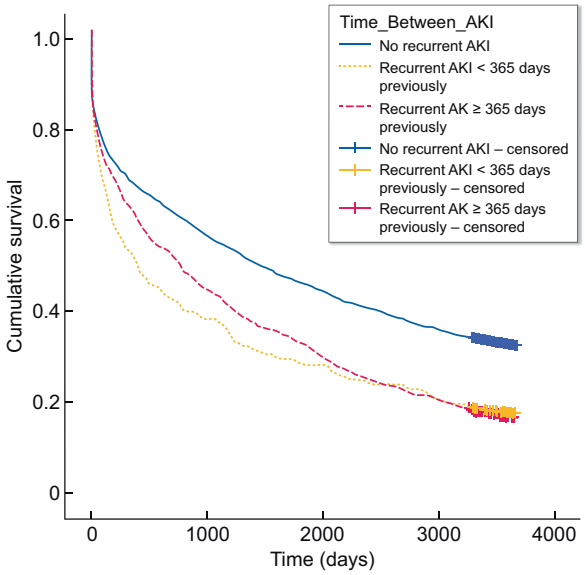

FIGURE 4: Kaplan–Meier plot of overall survival in patients with recurrent AKI with previous AKI <365 days previously compared with patients with recurrent AKI ≥365 days previously and patients with no evidence of recurrent AKI.

Overall, our results suggest that recurrent AKI is a marker of multi-morbidity and advancing age but when adjusting for these confounders, recurrent AKI also appears to be an independent risk factor for future mortality. The limitations of observational data and confounding have made it difficult to understand why AKI and recurrent AKI are associated with increased mortality. The prevention of recurrent AKI may have an impact on reducing future mortality but focusing on individual patient risk factors and comorbidities may also change how we manage such patients and plan future care.

Strengths of our study include a large sample size, assessing 136 448 eligible patients with 1 167 329 creatinine measurements and 3524 patients with AKI with a median follow-up of 3.17 years. We have used the standardized KDIGO definition of AKI and the widely used NHS England AKI algorithm to define AKI.

Our data also include patients that have had an AKI in the community as well as hospital-related AKI, which to our knowledge other studies have not [4, 5, 7, 9, 23]. This broad patient population allows for greater generalizability of the results. This study also has a number of limitations. The study is based on observational data and is therefore limited by confounding. AKI was defined using the creatinine-based component of the KDIGO definition. Urine output data are poorly recorded in the hospital setting and are not part of routinely collected data; therefore, we were unable to utilize this in defining cases of AKI, which may have been a more sensitive marker, and as a result we may have underestimated AKI. There are a number of other unmeasured confounders, including proteinuria prior to or follow AKI, hypertension, weight/BMI, smoking status, medications prescribed in hospital and cause of AKI that also limit the study.

A further limitation is that although we identified patients who had an AKI in 2009 and no previous evidence of AKI in the years 2003–08 prior to this, it is not possible to say that these patients did not have a further AKI event in the future prior to death or end of follow-up.

Table 2. Cox regression model for mortality

Variable	HR (95% CI)	P-value
Recurrent AKI	1.249 (1.141–1.368)	<0.001
No diabetes mellitus	1.00 (reference)	
Type 1 diabetes mellitus	0.975 (0.666–1/426)	0.895
Type 2 diabetes mellitus	0.981 (0.892–1.078)	0.686
AKI		
Stage 1	1.00 (reference)	
Stage 2	1.524 (1.369–1.696	<0.001
Stage 3	1.900 (1.673–2.158	<0.001
Sex (F = 0, M = 1)	1.220 (1.124–1.324)	<0.001
Age at last AKI event, years	1.045 (1.042–1.049)	<0.001
Diuretic	1.084 (0.993–1.182)	0.07
ACEi/ARB	0.716 (0.657–0.781)	<0.001
NSAIDS	0.808 (0.704–0.928)	0.002
β-blocker	0.893 (0.814–0.979)	0.016
Deprivation (least 1–3)	1.00 (reference)	
Deprivation (middle 4–7)	1.052 (0.96–1.153)	0.227
Deprivation (most 8–10)	1.159 (1.042–1.29)	0.007
MI	1.161 (10.38–1.298)	0.009
Peripheral vascular disease	1.305 (0.863–1.974)	0.207
Cerebrovascular disease	1.170 (1.057–1.296)	0.002
Baseline eGFR ≥60	1.00 (reference)	
Baseline eGFR 45–59	1.121 (1.002–1.255)	0.046
Baseline eGFR 30–44	1.236 (1.084–1.409)	0.002
Baseline eGFR 15–29	1.112 (0.901–1.372)	0.323
Baseline eGFR <15	0.984 (0.573–1.689)	0.953

This observational study suggests that increasing stage of reference AKI, increasing age, deprivation, lower baseline eGFR, previous MI and cerebrovascular disease, male sex and diuretic use were all associated with an increased risk of mortality in patients with recurrent AKI. After adjusting for patient characteristics and comorbidities the increase in mortality is independently associated with recurrent AKI and is not solely explained by other risk factors. This has implications for how we manage

and approach patients who experience multiple episodes of AKI. It is important that we focus on preventing AKI episodes as well as focusing on managing comorbidities that are likely to drive episodes of AKI and mortality.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to the study design, analysis of data, interpretation of results and drafting and revising this article. H.W. and S.B. designed the study including data collection, statistical analysis of the data and drafted and revised the article. N.D.S. designed and reviewed statistical analysis of the data and revised the draft article. M.D.W. was involved in study design and revised the draft article. S.H. was involved in the study design, statistical analysis and revision of the draft article. All authors agree to be accountable for ensuring all aspects of the work are accurate.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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