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Original Article

ORIGINAL ARTICLE

Acute kidney injury calculated using admission serum creatinine underestimates 30-day and 1-year mortality after acute stroke

Julia Arnold [1,2], Don Sims[3], Paramjit Gill[2,4], Paul Cockwell[1,2] and Charles Ferro [1,2]

[1]Department of Nephrology, University Hospitals Birmingham, Birmingham, UK, [2]College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [3]Department of Stroke, University Hospitals Birmingham, Birmingham, UK and [4]Warwick Medical School, University of Warwick, Coventry, UK

Correspondence and offprint requests to: Charles Ferro; E-mail: Charles.Ferro@uhb.nhs.uk

ABSTRACT

Background. Acute kidney injury (AKI) diagnosis requires ascertainment of change from a known baseline. Although pre-admission serum creatinine (SCr) is recommended, to date, all studies of AKI in acute stroke have used the first SCr on admission.

Methods. All patients admitted with an acute stroke to an emergency hospital were recruited. We compared use of pre-admission SCr with admission SCr to diagnose AKI. Regression analyses were used to identify risk factors for 30-day and 1-year mortality, respectively.

Results. A total of 1354 patients were recruited from December 2012 to September 2015. Incidence of AKI was 18.7 and 19.9% using pre-admission SCr and admission SCr, respectively. Diagnosis of AKI was associated with significantly increased 30-day and 1-year mortality. Diagnosis of AKI using pre-admission SCr had a stronger relationship with both 30-day and 1-year mortality. In 443 patients with a pre-admission SCr and at least two SCr during admission, AKI diagnosed using pre-admission SCr had a stronger relationship than AKI diagnosed using admission SCr with 30-day mortality [odds ratio (OR) = 2.64; 95% confidence interval (CI) 1.36–5.12; P = 0.004 versus OR = 2.10; 95% CI 1.09–4.03; P = 0.026] and 1-year mortality [hazard ratio (HR) = 1.90, 95% CI 1.32–2.76; P = 0.001 versus HR = 1.47; 95% CI 1.01–2.15; P = 0.046] in fully adjusted models.

Conclusions. AKI after stroke is common and is associated with increased 30-day and 1-year mortality. Using first SCr on admission gives a comparable AKI incidence to pre-admission SCr, but underestimates 30-day and 1-year mortality risk.

Keywords: acute kidney injury, mortality, stroke

INTRODUCTION

There is wide variation in the reported incidence of acute kidney injury (AKI) depending on definitions and populations studied: from 5.4% to 18.3% [1, 2] for hospitalized patients, to 40% in patients requiring intensive care [3, 4]. Having an episode of AKI is associated with increased mortality, inpatient length of stay and healthcare costs [5], and confers a higher risk of developing chronic kidney disease (CKD) [6] with its own sequelae.

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Currently, AKI diagnosis relies on the ascertainment of a peak increase in SCr from a known 'baseline' value [7]. The Acute Kidney Injury Network (AKIN) [8, 9] and European Renal Best Practice (ERBP) guideline [10] recommend the use of first SCr on admission. Kidney Disease: Improving Global Outcomes (KDIGO) recommends that AKI diagnosis requires knowledge of change in SCr from a known 'baseline' [7]. A developing consensus favours the use of an average SCr 7–365 days up to admission [8, 9, 11–15].

Stroke is the second most common cause of death and the leading cause of neurological disability worldwide [16]. Patients suffering a stroke are typically older, have significant co-morbidities and often have associated CKD [17, 18]. All of these features are recognized to be associated with AKI [3]. However, a recent systematic review and meta-analysis highlighted the fact that risk factors for AKI after a stroke have not been extensively investigated, and most studies have confined themselves to known generic risk factors for AKI [19]. Only two studies examined the association between stroke severity and AKI and only one study investigating the relationship between radiological contrast exposure and development of AKI [19]. Furthermore, no study has examined the association between thrombolysis, angiographic procedures or vascular interventions after an ischaemic stroke [19]. With an ageing population and increasing prevalence of CKD, together with an increasing use of interventional procedures, it is important to establish risk factors for, and the true incidence of, AKI after a stroke in order to design studies to potentially improve outcomes.

To date, all studies investigating AKI in acute stroke have used the first SCr result on admission [20–22]. No study has investigated the use of different methods to classify AKI and their relationship to outcomes in acute stroke. To address this, we sought to determine in a population of patients admitted with an acute stroke:

i. the incidence of AKI determined using pre-admission SCr compared with first SCr on admission;
ii. the risk factors for AKI in stroke patients; and
iii. the impact of AKI on mortality at 30 days and 1 year using different methods for AKI diagnosis.

MATERIALS AND METHODS

Study design and population

This was a prospective cohort study of patients presenting with an acute stroke (acute ischaemic stroke or intracranial haemorrhage) between December 2012 and September 2015 to an acute hospital in UK. Readmissions and patients with end-stage renal disease (ESRD) were excluded. A stroke physician assessed each case by history, neurological examination and brain imaging (computerized tomography and/or magnetic resonance imaging). We followed the STrengthening the Reporting of OBservational studies in Epidemiology guidelines [23].

Data collection and follow-up period

We used data from the Sentinel Stroke National Audit Programme [24]. Demographic data including age, sex, ethnicity, Index of Multiple Deprivation score, comorbidities [hypertension, diabetes mellitus, congestive heart failure, previous stroke or transient ischaemic attack (TIA) and atrial fibrillation (AF)] and stroke type were extracted from the database. Degree of disability was determined using the modified Rankin scale [25] and stroke severity using the National Institutes of Health Stroke Scale score [26]. Mortality data up to 1 year were collected from the Office of National Statistics [27]. Pre-admission SCr was calculated as the mean of all pre-admission SCr values 7–365 days before admission [15].

Impaired renal function was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration and subdivided into GFR categories as per KDIGO CKD Guidelines [28]. For patients with no pre-admission SCr, impaired renal function was defined as an eGFR <60 mL/min/1.73 m^2 using the first SCr value on admission. Anaemia was defined as a haemoglobin level <135 g/L for males and <115 g/L for females as per laboratory reference ranges.

Patients were divided into three groups depending on the availability of SCr data (Figure 1): Group A: all patients with at least one pre-admission SCr available in the 7–365 days preceding admission; Group B: all patients with at least two SCr available after admission; and Group C: all patients that that fulfilled criteria for Groups A and B. Patients could therefore be assigned to more than one group.

Ethical approval was granted for this study (East of England–Essex Research Ethics Committee 16/EE/0166).

Definition of AKI

The rate of AKI using pre-admission SCr (termed AKI^{pre}) was compared with the surrogate, first SCr on hospital admission (termed AKI^{adm}). AKI was defined as per KDIGO guidelines [7]. Urine output criteria were not used since electronic records of urine output were incomplete.

Statistical analysis

Analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ±standard deviation (SD) for normally distributed variables or median and interquartile range for non-normally distributed variables and compared using the *t*-test or Mann–Whitney U test. Categorical variables are expressed as proportions and compared using the Chi-squared test or McNemar test for dichotomous variables [29]. All variables used in the analysis had <5% of values missing and were therefore treated as missing completely at random with case-wise deletion.

AKI^{pre} and AKI^{adm} methods were compared using the Bland–Altman method [30]. Sensitivity and specificity were reported for each method with the kappa value and 95% confidence intervals (CIs) used to denote the level of agreement between different methods. We calculated misclassification rates as the proportion of patients incorrectly assigned as having AKI as compared with AKI^{pre} and compared correctly classified and misclassified AKI using the McNemar test.

Kaplan–Meier survival curves were drawn to assess group differences for time-to-event data and compared using the Log rank test. Logistic regression was used to assess the relationship between outcomes and parameters under investigation, expressed as an odds ratio (OR) with 95% CI. Time-to-event analysis for cumulative 1-year mortality was performed using the Cox proportional hazards model and results expressed as a hazard ratio (HR) with 95% CI. Variables found to be associated with the outcome under investigation in the univariable analysis were included in the multivariable models. A P-value threshold of <0.15 was selected in order to retain all potential risk factors and minimize the chance of type II errors [31].

RESULTS

In total, 1440 hospital admissions with acute stroke occurred within the study period (Figure 1). From these, 52 patients who

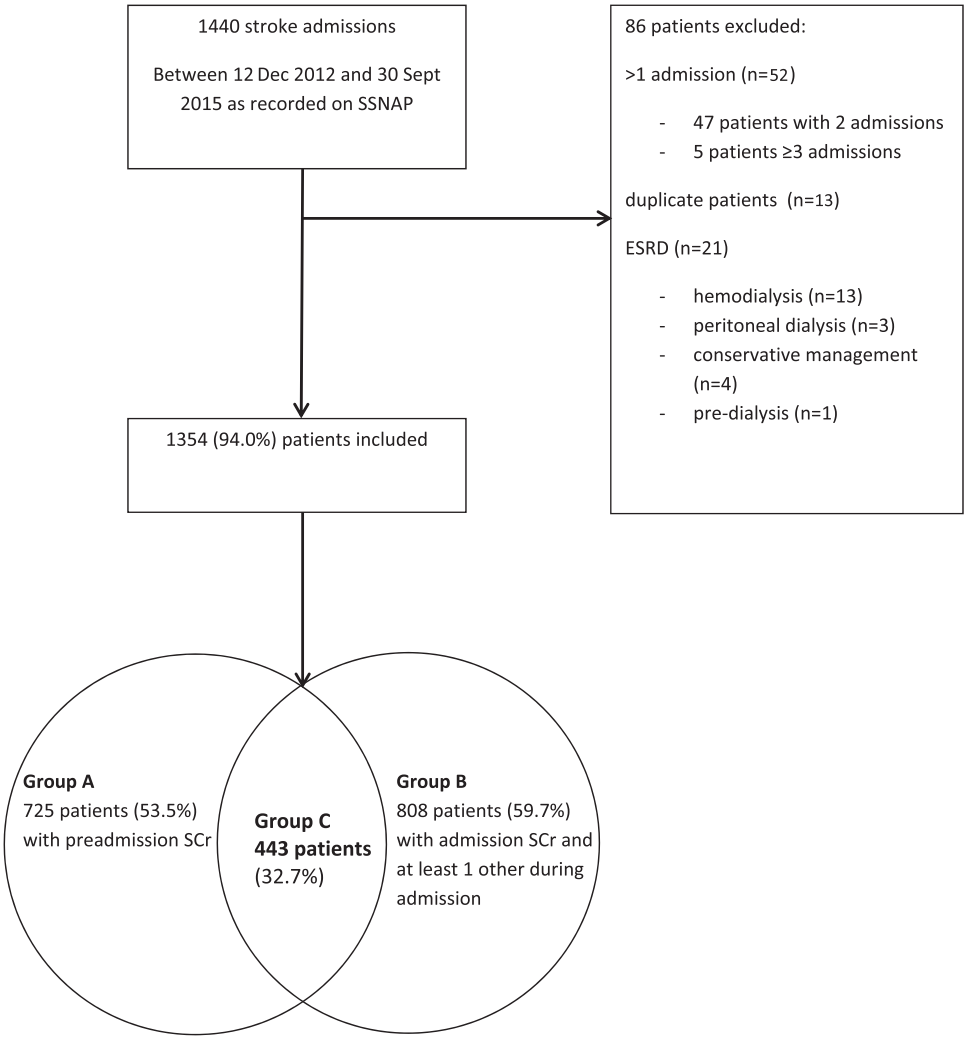

FIGURE 1: Study flow diagram. SSNAP, Sentinel Stroke National Audit Programme.

were readmitted over the same period were excluded, as well as 13 duplicates and 21 patients with ESRD. The remaining 1354 patients were included for analysis. Among these patients, 725 (53.5%) fulfilled criteria for inclusion in Group A, 808 (59.7%) for Group B and 443 (32.7%) for Group C.

Characteristics of patients with and without pre-admission SCr

The baseline characteristics of the study population with and without pre-admission SCr data are shown in Table 1. In multivariable analysis, patients with pre-admission SCr values were more likely to be older, of non-Black ethnicity, have a concurrent diagnosis of diabetes mellitus, AF, previous stroke or TIA, and have higher disability on admission (Supplementary data, Appendix S1).

AKI diagnosis

Rates of AKI using AKI^{pre} and AKI^{adm} were compared in patients in Group C. There was no difference in the rates of AKI using AKI^{pre} or AKI^{adm} (18.7% versus 19.9%; $P = 0.63$). The rates of AKI and agreement between methods are summarized in Supplementary data, Appendix S2. The overall misclassification rate was 17.4% (Kappa statistic 0.46 with 9.7% of cases overclassified and 7.7% of cases underclassified as having AKI) (Supplementary data, Appendix S3). A Bland–Altman plot (Supplementary data, Appendix S4) showed the majority of values fall within the limits of agreement.

Comparison of pre-admission SCr and admission SCr

In Group C, 25.1% had a first admission SCr that was ≥110% above the pre-admission SCr (Supplementary data, Appendix S5). A greater proportion of patients classified as having AKI^{pre} experienced this pattern compared with patients classified as having AKI^{adm} (48.2 and 20.5%, respectively). Conversely, 23.9% had a first admission SCr that was ≤90% of the pre-admission SCr with a greater proportion of patients with AKI^{adm} compared with AKI^{pre} experiencing this pattern (33.0 and 12.0%, respectively). Similar results were obtained in Group A (Supplementary data, Appendix S6).

Factors associated with AKI

In Group C, factors associated with AKI^{pre} and AKI^{adm} in multivariable analyses (Supplementary data, Appendix S7) were the presence of an eGFR <60 mL/min/1.73 m^2 (OR = 2.78; 95% CI

Table 1. Baseline characteristics according to presence of pre-admission SCr

Parameters	With pre-admission SCr ($n = 725$)	Without pre-admission SCr ($n = 629$)
Age, years, mean (SD)	74.83 (14.09)	69.04 (16.33)
Male (%)	366 (50.5)	362 (57.6)
Ischaemic stroke (%)	643 (88.7)	553 (87.9)
NIHSS score on admission, median (IQR)	3.0 (8)	4.0 (8)
NIHSS level of consciousness (0–3), median (IQR)	0 (0)	0 (0)
IMD score, mean (SD)	30.51 (15.37)	30.60 (17.82)
Ethnic group (%)		
White	625 (86.2)	505 (80.3)
Asian/Asian British	68 (9.4)	61 (9.7)
Black/Black British	18 (2.5)	32 (5.1)
Mixed/other/unknown	14 (1.9)	31 (4.9)
Pre-admission SCr, mean (SD) (μmol/L)	91.32 (31.40)	–
Pre-admission eGFR, mean (SD) (mL/min/1.73 m^2)	68.45 (22.72)	–
Admission SCr, mean (SD) (μmol/L)	91.15 (41.55)	84.14 (24.78)
Admission eGFR, mean (SD) (mL/min/1.73 m^2)	67.90 (22.71)	75.84 (22.35)
Pre-admission eGFR <60 mL/min/1.73 m^2 (%)	278 (38.3)	–
Admission eGFR <60 mL/min/1.73 m^2 (%)	275 (37.9)	159 (25.3)
Hypertension (%)	378 (52.1)	273 (43.4)
Diabetes mellitus (%)	175 (24.1)	105 (16.7)
CHF (%)	35 (4.8)	17 (2.7)
Previous stroke/TIA (%)	218 (30.1)	122 (19.4)
AF (%)	179 (24.7)	75 (11.9)
Thrombolysis (%)	64 (8.8)	105 (16.7)
Thrombectomy (%)	14 (1.9)	38 (6.0)
Any iodinated contrast exposure (%)	130 (17.9)	151 (24.0)

Data are presented as mean ± SD, median (IQR) or *n* (%).
CHF, congestive heart failure; IMD, Index of Multiple Deprivation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

1.69–4.57; P <0.001 and OR = 2.60; 95% CI 1.60–4.23; P < 0.001, respectively) and anaemia (OR = 1.78; 95% CI 1.06–2.97; P = 0.03 and OR = 1.96; 95% CI 1.19–3.24; P = 0.009, respectively). Similar associations were found in Group A for AKI^{pre} (Supplementary data, Appendix S8) and in Group B for AKI^{adm} (Supplementary data, Appendix S9).

AKI and 30-day mortality

In Group A, 30-day mortality was significantly higher in patients with AKI^{pre} compared with patients without AKI [(24/88) 27.3% versus (66/637) 10.5%; P <0.001]. In Group B, the mortality rate was also higher in the AKI^{adm} group [(27/134) 20.1% versus (82/674) 12.2%; P = 0.01]. In Group C, mortality was higher in the AKI group when both AKI^{pre} [(24/83) 28.9% versus (50/360) 13.9%; P = 0.001] and AKI^{adm} [(21/88) 23.9% versus (53/355) 14.9%; P = 0.04] were used to identify AKI compared with patients without AKI.

The full univariable and multivariable associations with 30-day mortality in Groups A and B are shown in Supplementary data, Appendices S10 and S11. In Group A, AKI^{pre} was associated with 30-day mortality in multivariable analysis (OR = 2.66; 95% CI 1.40–5.05; P = 0.003; Table 2). In Group B, AKI^{adm} was associated with 30-day mortality in multivariable analysis (OR = 1.79; 95% CI 1.04–3.08; P = 0.04; Table 2).

The full univariable and multivariable associations with 30-day mortality in Group C are shown in Supplementary data, Appendix S12. Both AKI^{pre} (OR = 2.64; 95% CI 1.36–5.12; P = 0.004) and AKI^{adm} (OR = 2.10; 95% CI 1.09–4.03; P = 0.03) remained associated with 30-day mortality in the adjusted models (Table 2). Given that AKI^{pre} appeared to have a stronger relationship with 30-day mortality than AKI^{adm}, we constructed further models adjusting for factors associated with 30-day mortality when either AKI^{pre} or AKI^{adm} were used in the multivariable model. The OR for mortality remained higher using AKI^{pre} than AKI^{adm} in all models (Models 3–5; Table 2). We created additional models by entering both AKI^{pre} and AKI^{adm}. In all models, only AKI^{pre} was retained (Models 6–10; Table 2), suggesting that AKI^{pre} does indeed have a stronger relationship with 30-day mortality than AKI^{adm}. We further explored this relationship by forcing AKI^{adm} into the multivariable models and then adding AKI^{pre}. In all cases, AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{adm} alone (Models 11–15; Table 2).

AKI and 1-year mortality

In Group A, 1-year mortality was significantly higher in patients with AKI^{pre} compared with patients without AKI [(42/88) 47.7% versus (131/637) 20.8%; P <0.001]. In Group B, the mortality rate was higher in the AKI^{adm} group [(51/134) 38.1% versus (156/674) 23.1%; P <0.001]. In Group C, mortality was higher in the AKI group when both AKI^{pre} [(42/83) 50.6% versus (97/360) 26.9%; P <0.001] and AKI^{adm} [(38/88) 43.2% versus (101/355) 28.5%; P <0.001] were used to identify AKI compared with patients without AKI (Figure 2).

The full univariable and multivariable associations with 1-year mortality in Groups A and B are shown in Supplementary data, Appendices S13 and S14. In Group A, AKI^{pre} was associated with 1-year mortality in multivariable analysis (HR = 2.00; 95% CI 1.40–2.86; P <0.001; Table 3). In Group B, AKI^{adm} was associated with 1-year mortality in multivariable analysis (HR = 1.50; 95% CI 1.10–2.07; P = 0.01; Table 3).

The full univariable and multivariable associations with 1-year mortality in Group C are shown in Supplementary data,

Table 2. Logistic univariable and multivariable associations of AKI calculated using pre-admission SCr (AKI^{pre}) or admission creatinine (AKI^{adm}) with 30-day mortality

Models	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	OR	P-value	OR	P-value	OR	P-value	OR	P-value
Model 1	3.21 (1.88–5.48)	<0.001	1.82 (1.13–2.95)	0.015	2.52 (1.44–4.42)	0.001	1.79 (1.01–3.16)	0.046
Model 2	2.86 (1.65–4.98)	<0.001	1.58 (0.96–2.60)	0.07	2.37 (1.33–4.22)	0.003	1.71 (0.95–3.07)	0.07
Model 3	2.66 (1.40–5.05)	0.003	1.79 (1.04–3.08)	0.04	2.64 (1.36–5.12)	0.004	2.10 (1.09–4.03)	0.03
Model 4	2.66 (1.40–5.05)	0.003	1.79 (1.04–3.08)	0.04	2.64 (1.36–5.12)	0.004	2.10 (1.09–4.03)	0.03
Model 5	2.66 (1.40–5.05)	0.003	1.79 (1.04–3.08)	0.04	2.64 (1.36–5.12)	0.004	2.10 (1.09–4.03)	0.03
Model 6	–	–	–	–	2.52 (1.44–4.42)	0.001		
Model 7	–	–	–	–	2.37 (1.33–4.22)	0.003		
Model 8	–	–	–	–	2.64 (1.36–5.12)	0.004		
Model 9	–	–	–	–	2.64 (1.36–5.12)	0.004		
Model 10	–	–	–	–	2.64 (1.36–5.12)	0.004		
Model 11	–	–	–	–	AKI^{adm} 1.13 (0.57–2.25) AKI^{pre} 2.37 (1.21–4.62)	0.73 0.01	–	–
Model 12	–	–	–	–	AKI^{adm} 1.09 (0.54–2.22) AKI^{pre} 2.323 (1.160–4.650)	0.81 0.02	–	–
Model 13	–	–	–	–	AKI^{adm} 1.35 (0.61–3.01) AKI^{pre} 2.20 (1.00–4.84)	0.46 0.051	–	–
Model 14	–	–	–	–	AKI^{adm} 1.38 (0.62–3.10) AKI^{pre} 2.22(1.00–4.91)	0.43 0.049	–	–
Model 15	–	–	–	–	AKI^{adm} 1.35 (0.60–3.02) AKI^{pre} 2.25 (1.02–4.97)	0.47 0.046	–	–

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, presence of eGFR <60 mL/min/1.73 m^2 and AF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group A). Model 4: adjusted for age, sex, ethnicity, presence of eGFR <60 mL/min/1.73 m^2, AF and hypertension, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group B). Model 5: adjusted for age, sex, ethnicity, presence of eGFR <60 mL/min/1.73 m^2, AF and hypertension, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Groups A and B). Model 6: Model 1 + AKI^{pre} and AKI^{adm}. Model 7: Model 2 + AKI^{pre} and AKI^{adm}. Model 8: Model 3 + AKI^{pre} and AKI^{adm}. Model 9: Model 4 + AKI^{pre} and AKI^{adm}. Model 10: Model 5 + AKI^{pre} and AKI^{adm}. Model 11: Model 6 with AKI^{adm} forced into model. Model 12: Model 7 with AKI^{adm} forced into model. Model 13: Model 8 with AKI^{adm} forced into model. Model 14: Model 9 with AKI^{adm} forced into model. Model 15: Model 10 with AKI^{adm} forced into model.

Appendix S15. Both AKI^{pre} (HR = 1.90; 95% CI 1.32–2.76; P = 0.001) and AKI^{adm} (HR = 1.47; 95% CI 1.01–2.15; P = 0.05) remained associated with 1-year mortality in the adjusted models (Table 3). Similar to 30-day mortality, AKI^{pre} appeared to have a stronger relationship with 1-year mortality than AKI^{adm}, and further models were constructed adjusting for factors associated with 1-year mortality when either AKI^{pre} or AKI^{adm} were used in the multivariable model (Table 3). The HR for mortality remained higher using AKI^{pre} than AKI^{adm} in all models (Models 3–5; Table 3). We created additional models by entering both AKI^{pre} and AKI^{adm}. In all models, only AKI^{pre} was retained (Models 6–10; Table 3), suggesting AKI^{pre} does indeed have a stronger relationship with 30-day mortality than AKI^{adm}. We further explored this relationship by forcing AKI^{adm} into the multivariable models and then adding AKI^{pre}. In all cases, AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{adm} (Models 11–15; Table 3).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the rate of AKI in acute stroke utilizing two different methods. We show that AKI in unselected patients hospitalized after a stroke is high at ~20% and this rate does not appear to be dependent on the method used to diagnose AKI. We also show that mortality after AKI is high but consistently higher in AKI^{pre}, with 27.3 and 47.7% of patients being dead at 30 days and 1 year, respectively. Use of AKI^{adm} consistently underestimates mortality risk at both time points.

SCr is an imperfect measurement of dynamic glomerular filtration rate [32] and is modified by age, sex and race as well as nutritional state, muscle mass and hydration [3]. Consequently, novel biomarkers for earlier and more accurate detection of AKI are under investigation, but to date, these have not progressed to use in routine medical practice [33–36]. Therefore, SCr remains the only routinely used laboratory test for the diagnosis of AKI [37–39].

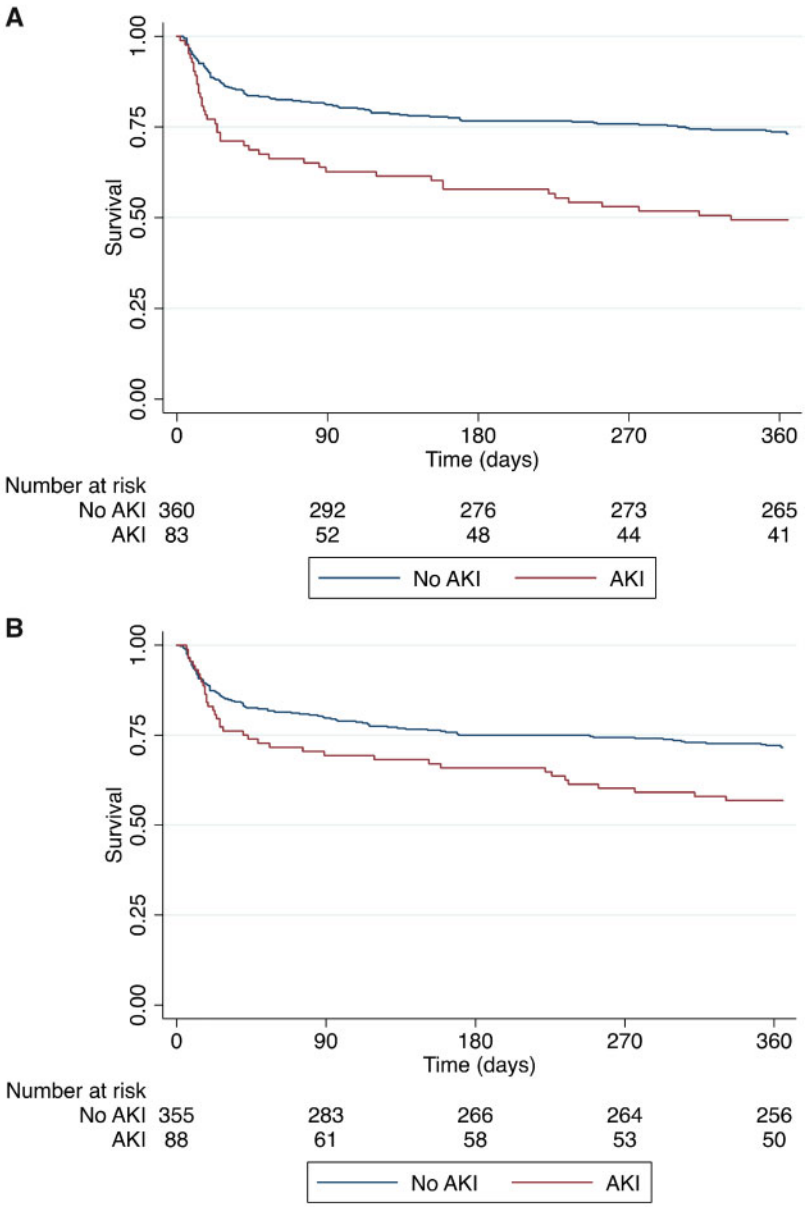

FIGURE 2: (**A**) Kaplan–Meier survival curve at 365 days for Group C using AKI^{pre} to diagnose AKI rates. Log rank test = 19.73; $P < 0.001$. (**B**) Kaplan–Meier survival curve for Group C at 365 days using AKI^{adm} to diagnose AKI. Log rank test = 6.93; $P = 0.008$.

Use of admission SCr, as recommended by AKIN [8, 9] and ERBP guidelines [10], to diagnose AKI has low sensitivity and may therefore fail to detect both community-acquired and hospital-acquired AKI [40]. Use of a baseline SCr taken 7–365 days up to admission [8, 9, 11–15] is not available for many patients because of the absence of a pre-admission value. In our cohort, 46.5% of patients did not have a pre-admission SCr, consistent with published data [41], and we found that patients with a pre-admission SCr were more likely to be older and have more comorbidities. Although we have performed several analyses to exclude this as a major source of confounding, it remains possible that some residual confounding persists and our findings require confirmation in other studies. Patients of black ethnicity were less likely to have a pre-admission SCr, consistent with reports that this ethnic group is less likely to have access to health systems both in the USA and the UK [42–44]. This has partly been attributed to socioeconomic status [45]. However, in this study, socioeconomic deprivation did not appear to be associated with having a pre-admission SCr. It is uncertain whether this is a factor of the UK's social system of healthcare or whether it would be replicated in other healthcare systems [44].

Using admission SCr to diagnose AKI in our cohort produced a similar rate of AKI to pre-admission SCr. These rates are comparable to other published studies that utilize SCr values rather than coding to diagnose AKI, with rates ranging from 15% to 27% [20–22]. However, although the absolute rates are similar, AKI^{adm} when compared with AKI^{pre} had low sensitivity and a Kappa value indicating only moderate agreement. We also found that individual patients were just as likely to have a SCr on admission that was 10% higher or 10% lower than the pre-admission SCr. This could potentially suggest a random effect consistent with day-to-day biological fluctuations in SCr [46, 47]

Table 3. Cox univariable and multivariable associations of AKI calculated using pre-admission SCr (AKI^{pre}) or admission creatinine (AKI^{adm}) with 1 year mortality

Models	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	HR	P-value	HR	P-value	HR	P-value	HR	P-value
Model 1	2.74 (1.937–3.886)	<0.001	1.77 (1.29–2.42)	<0.001	2.22 (1.55–3.19)	<0.001	1.64 (1.13–2.38)	0.009
Model 2	2.43 (1.72–3.45)	<0.001	1.52 (1.11–2.09)	0.009	2.08 (1.44–2.99)	<0.001	1.55 (1.07–2.26)	0.02
Model 3	2.00 (1.40–2.86)	<0.001	1.50 (1.10–2.07)	0.01	1.98 (1.37–2.85)	<0.001	1.53 (1.05–2.23)	0.03
Model 4	2.00 (1.40–2.86)	<0.001	1.50 (1.10–2.07)	0.01	1.98 (1.37–2.85)	<0.001	1.53 (1.05–2.23)	0.03
Model 5	2.00 (1.40–2.86)	<0.001	1.50 (1.10–2.07)	0.01	1.90 (1.32–2.76)	0.001	1.47 (1.01–2.15)	0.05
Model 6	–	–	–	–	2.22 (1.55–3.19)	<0.001		
Model 7	–	–	–	–	2.08 (1.44–2.99)	<0.001		
Model 8	–	–	–	–	1.98 (1.37–2.85)	<0.001		
Model 9	–	–	–	–	1.98 (1.37–2.85)	<0.001		
Model 10	–	–	–	–	1.90 (1.32–2.76)	0.001		
Model 11	–	–	–	–	AKI^{adm} 1.11 (0.71–1.74) AKI^{pre} 2.10 (1.36–3.25)	0.65 0.001	–	–
Model 12	–	–	–	–	AKI^{adm} 1.07 (0.68–1.66) AKI^{pre} 2.06 (1.33–3.18)	0.78 0.001	–	–
Model 13	–	–	–	–	AKI^{adm} 1.09 (0.69–1.72) AKI^{pre} 2.02 (1.29–3.17)	0.70 0.002	–	–
Model 14	–	–	–	–	AKI^{adm} 1.07 (0.68–1.70) AKI^{pre} 1.96 (1.25–3.08)	0.76 0.004	–	–
Model 15	–	–	–	–	AKI^{adm} 1.06 (0.67–1.68) AKI^{pre} 2.00 (1.27–3.16)	0.81 0.003	–	–

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, presence of eGFR <60 mL/min/1.73 m^2, AF and CHF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1-year mortality in Group A). Model 4: adjusted for age, sex, presence of eGFR <60 mL/min/1.73 m^2 and AF, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1-year mortality in Group B). Model 5: Model 3 plus ethnicity. Model 6: Model 1 + AKI^{pre} and AKI^{adm}. Model 7: Model 2 + AKI^{pre} and AKI^{adm}. Model 8: Model 3 + AKI^{pre} and AKI^{adm}. Model 9: Model 4 + AKI^{pre} and AKI^{adm}. Model 10: Model 5 + AKI^{pre} and AKI^{adm}. Model 11: Model 6 with AKI^{adm} forced into model. Model 12: Model 7 with AKI^{adm} forced into model. Model 13: Model 8 with AKI^{adm} forced into model. Model 14: Model 9 with AKI^{adm} forced into model. Model 15: Model 10 with AKI^{adm} forced into model.

or analytical variability in the laboratory [48]. Consistent with this, we found that patients with a higher admission SCr were more likely to be diagnosed with AKI^{pre}, whereas patients with a lower admission SCr were more likely to be diagnosed with AKI^{adm}. Despite the similar rates of AKI diagnosed with either method, we found that AKI^{pre} was consistently associated with higher 30-day and 1-year mortality than AKI^{adm}. Although we cannot prove this conclusively, our results would suggest that using AKI^{pre} correctly identifies more patients with 'true' AKI. Furthermore, our finding that AKI^{pre} was associated with a higher mortality risk than AKI^{adm} indicates that AKI-associated mortality in acute stroke, as reported to date, probably underestimates the association, given that all of the studies that used SCr to define AKI used first SCr on admission [20–22]. These findings have major implications for clinical management and further research. Future epidemiological, or indeed interventional studies, should make every effort to use pre-admission SCr as the baseline for AKI diagnosis.

In some clinical situations, where the first SCr on admission is taken as the baseline value, cases of community-acquired AKI may be missed, thus underestimating AKI incidence [8]. Conversely, in older and frailer patients with an acute illness, the admission SCr may be lower than the outpatient 'baseline', leading to overestimation of AKI rates [14, 49]. Inclusion of patients without true AKI in the analysis may introduce further bias. This was emphasized by a recent US study which reported that 45% of all hospitalized patients had a first SCr on admission <90% of the pre-admission SCr [14]. However, we feel that these are unlikely to have been significant factors in our study. Acute stroke, by its very nature, happens suddenly and patients are usually admitted to hospital almost immediately, giving little time to develop community-acquired AKI. Patients presenting with a first acute stroke might also be less likely to have a gradually worsening health state preceding the admission, and therefore less likely to have a lower SCr as might be expected in patients with more chronic conditions.

Our study has some limitations to acknowledge. A significant proportion of the cohort had no pre-admission SCr. This may have caused confounding since patients with available pre-admission SCr likely represent a more comorbid group. To

address this, we selected a core cohort of patients (Group C) who had both a pre-admission SCr value and at least two blood tests during admission and used multiple adjustments in our analysis. However, it is possible that residual confounding remains. We do not have data on the length of time between the onset of the acute stroke and the drawing of blood for measurement of SCr. However, patients suffering an acute stroke are generally admitted to hospital immediately and blood drawn shortly after arrival in the emergency department. Therefore, the interval is unlikely to be ever more than a few hours and it is doubtful that this would have a significant effect on the findings. We do not have data on cause of death. There is surprisingly little data on the cause of death after AKI. A recent population-based study has shown that the most common causes of death after AKI are cancer or cardiovascular events [50]. We would therefore predict that cardiovascular events were the most common cause of death after AKI in stroke patients, but further work is required to prove this. Our study utilizes data from a cohort of stroke patients and therefore AKI incidence, risk factors and outcomes may be different to an unselected hospital population with AKI. Finally, we were limited by the observational nature of this study and were unable to address causality.

CONCLUSIONS

In summary, AKI after stroke is common and associated with increased mortality. First creatinine on admission gives a comparable incidence of AKI to pre-admission creatinine but with low sensitivity. First creatinine on admission to classify AKI consistently underestimates 30-day and 1-year mortality compared with pre-admission SCr. Further studies are required to help inform future AKI prevention trials that are urgently needed to ultimately improve clinical outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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