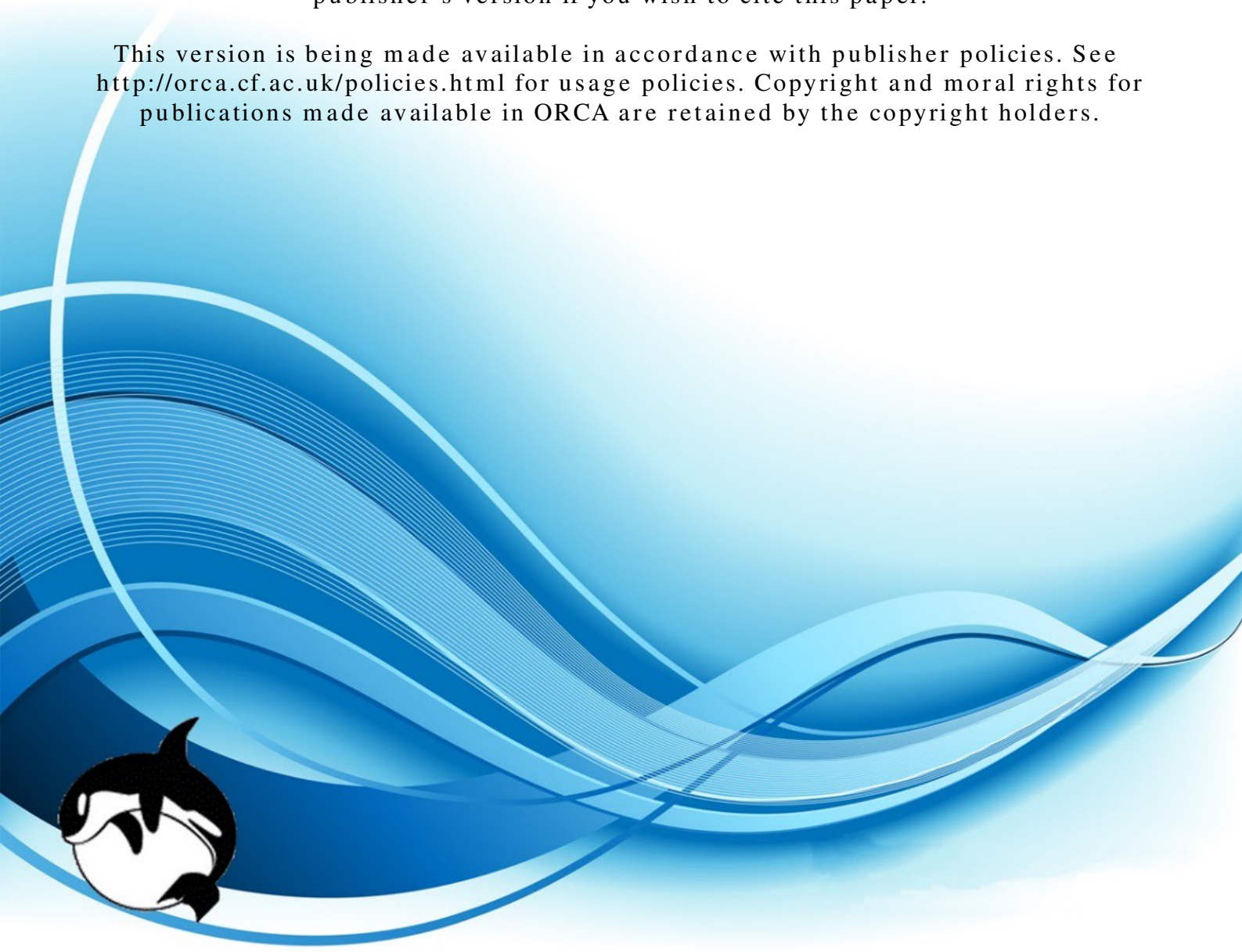

Acute Kidney Injury in Paediatrics based on electronic AKI alerts.

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Abstract

Objective: Our aim was to define the incidence and outcome of AKI in paediatrics using data collected from a national electronic alert system.

Design: A prospective national cohort study was undertaken to collect data on all cases of paediatric AKI, excluding neonates, identified by an e-alert, from April 2015 to March 2019.

Results: There were 2472 alerts in a total of 1719 patients, giving an incidence of 77.3 per 100,000 person-years. 84.2% of all AKI were stage 1, and 58.3% occurred with a triggering creatinine within the reference range. The incidence of AKI was associated with measures of social deprivation. 30-day mortality was 1.7%, but was significantly higher in HA-AKI (2.1%), compared to CA-AKI (0.8%, P<0.001) and was associated with the severity of AKI at presentation. A significant proportion of patients had no repeat measure of creatinine (39.8%). This was higher in CA-AKI (69.7%) compared to HA-AKI (43.0%, P<0.001), and higher in patients alerting with patients triggering with a creatinine within the reference range (48.4% vs. 24.5%, P<0.001). The majority of patients (84.7%) experienced only one AKI episode. Repeated episodes of AKI were associated with increased 30-mortaltiy (11.6% vs. 4.6%, P<0.001) and higher residual renal impairment (13.3% vs. 5.4%, p<0.001).

Conclusions The results suggest that the significance of the alert is missed in many cases reflecting that a large proportion of cases represent modest elevations in serum creatinine, triggered by a serum creatinine which may be interpreted as being normal despite a significant increase from the baseline for the patient.

Introduction

AKI in children is associated with prolonged hospital stay [1], higher in-patient mortality [2], long term renal dysfunction [3]. Using a centralised system of data collection, based on an electronic AKI alert, we have published a detailed characterisation of the epidemiology of AKI in adults [4-11]. Our previous data in a small paediatric cohort demonstrated that over 40% of paediatric cases of AKI occurred in neonates [12]. In the current study, we provide a detailed characterisation of AKI, in what is to our knowledge the largest cohort of non-neonatal paediatric patients reported to date.

Methods

Data was collected on all AKI cases in patients under the age of 18 identified by an AKI e-alert between April 2015 and March 2019. Patients aged ≤28 days were excluded. The study was approved under the terms of Service Evaluation Project Registration.

The Welsh electronic AKI reporting system [4] utilises the all Wales Laboratory Information Management System (LIMS), (InterSystems TrakCare Lab) to compare measured serum creatinine (SCr) values on an individual against previous results for the same patient, in real time, to generate alerts using an algorithm based on changes in SCr level and KDIGO AKI staging criteria (Figure 1 - On line only). A summary of the definitions of AKI stages is shown in table 1 (on line). Stage 1 AKI represents an increase of serum creatinine ≥26μmol/l or an increase 1.5 to 1.9 times the reference creatinine. Stage 2 represents an increase 2 to 2.9 fold the reference

creatinine and stage 3 AKI ≥ 3 times the reference creatinine or a rise of ≥1.5 baseline to > 354mmol/l. AKI alerts are generated by applying three "rules" based on on the time period from which the baseline creatinine is obtained. The e-alert rule and the comment accompanying the e-alert is shown in Table 2 (on line). Rule 2 alerts represent a ≥50% increase in SCr within 7 days, a rule 3 alert a ≥50% increase in SCr from the median of results of the previous 8 to 365 days, and rule 1 alerts a >26μmol/L increase in SCr within the previous 48 hours but only if rule 2 and rule 3 are not satisfied. The e-alert code together with the comment which accompanies the e-alert is shown in Table 3 (on line). This system encompasses all laboratory tests done in Wales, regardless of the patient location and the ordering clinician. The alert is transmitted with the result of the serum creatinine as a 'flag" that states that the result is abnormal and in keeping with AKI. The AKI stage is also reported and the alert signposts the reviewing clinician to the Welsh AKI clinical management guidelines. Creatinine is measured using kinetic Jaffe methodology, standardised using ID/MS calibrated reference material.

Result of renal transplant and dialysis patients, and alerts generated in renal wards were excluded to avoid false positive AKI alerts resultant from fluctuations in creatinine related to dialysis. Data were collected on age, gender, stage of index AKI episode and the clinical location at which the alert was generated. An AKI episode was defined as a period of 30 days.

Hospital acquired (HA-AKI) was defined as AKI triggered by an alert in an inpatient setting. Patients alerting in non-inpatient settings were classified as Community Acquired AKI (CA-AKI), this includes, primary care, and all non in-patient settings of secondary care. Patients were labelled as Hospitalization of CA-AKI if a patient had a

previous measurement of renal function in an inpatient setting within 7 days of the incident alert. To determine if the AKI alert was generated by a serum creatinine value within the normal reference range, the serum creatinine reference ranges for age and sex currently in use in Wales were used[13] Table 4 (on line).

Data on patient mortality were collected from the Welsh Demographic Service [14] and expressed as either 30-day mortality or Kaplan-Meier curves with data censored at 4 years. Recovery was defined as achievement of a serum creatinine (SCr) value during the episode no longer in keeping with the definition of AKI when compared with the baseline SCr (bSCr) value which generated the alert. Patients were included in 30-day renal outcome analysis if they survived the episode and had follow up data available. For repeat AKI episodes, recovery was defined as achievement of a SCr value no longer in keeping with the definition of AKI when compared with bSCr value which generated the incident alert.

Social deprivation was determined by the Welsh Index of Multiple, which ranks each of 1,909 geographical areas in Wales, based on Income, Employment, Health, Education, Access to Services, Community Safety, Physical Environment, Housing to generate a WIMD score [15]. Patients were categorised according to their area of residence, and ranked into deciles of WIMD score (decile 1 being the most deprived). Incidence was derived from Mid-2013 ONS Population Estimates [16], using the total paediatric population in each of the geographical areas of residence from which the WIMD score was generated.

Statistical analysis was carried out using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student's t-test was used for analysis of normally distributed data. Categorical data were compared using a Pearson chi-squared test. Data is expressed

as mean ±SD, p values less than 0.05 were considered statistically significant.

Results

There were 2472 alerts in a total of 1719 patients (Table 5), giving an incidence of 77.3 per 100,000 person-years. The mean age of patients was 7.3±6.1 years. Acute on Chronic renal impairment represented 3.8% of cases. The majority of cases were AKI stage 1 (84.2%), with 12.3% presenting as AKI stage 2 and only 3.6% as AKI stage 3. There was a negative correlation between WIMD score and the incidence of AKI (Figure 2A), with the highest incidence rates associated with the highest measures of social deprivation (r=-0.91, 95% CI -0.94 to -0.87 p<0.001).

30-day mortality was 1.7% (Table5) and overall mortality was 5.67%. Higher mortality was associated with stage 2 or 3 AKI compared to stage 1 (3.9 vs. 1.3%, P<0.001). In the surviving group severity of AKI was also a determinant of recovery of renal function, with recovery of renal function lower in patients with incident stage 2 or 3 AKI alerts compared with stage 1 (85.9 vs. 95.9%, P<0.001). The likelihood of a repeat measure of creatinine, was higher for patients presenting with stage 2 or 3 AKI compared to stage 1 (72.3 vs. 59.1%, P<0.001), although even for patients with an incident AKI stage 2/3, 27.7% of patients had no repeat measurement of creatinine within 30 days of the incident AKI alert.

Comparison of hospital and community acquired AKI

Compared to the CA-AKI acquired cohort, the HA-AKI group were younger (HA-AKI: 6.3±5.7 vs. CA-AKI: 9.4±6.3 years, P<0.001), and had a higher proportion of males

HA-AKI: 55.1 vs. CA-AKI: 44.3%, P<0.001). There was no difference in severity of AKI as assessed by AKI stage at presentation between HA and CA groups.

Compared to CA-AKI, 30-day mortality was significantly higher for patients following HA-AKI (HA-AKI: 2.1% vs. CA-AKI: 0.8%, P<0.01). Mortality censored at 4 years was also significantly greater in the HA-AKI (HA-AKI: 7.4% vs. CA-AKI: 1.9%, P <0.001 Figure 2B). In contrast to mortality outcomes, for the surviving patients, recovery of renal function at 30-days was significantly better following HA-AKI (HA-AKI; 95.0 vs. CA-AKI: 90.7%, P<0.05).

Significantly more patients in the HA-AKI group had a repeat measurement of creatinine in the 30-day period following the alert, (69.7% vs. 43.0%, P<0.001). For those with a repeat measure of creatinine, the time to repeat was also shorter in the HA-AKI group (2.7 ±5.0 vs. 3.4 ± 6.0 days, P<0.01).

Accident and Emergency, Outpatients and General Practice accounted for 86.1% of all CA-AKI alerts (Table 6 – on line). Admission to hospital following a CA-AKI alert, was highest following an A+E alert (40.5%). There was no difference in admission rates following OPD or GP alerts (14.0 vs. 7.1%, P>0.05). It is of note that all 9 patients admitted following a GP alert, presented with a stage 1 AKI alert, whilst 12 patients (9.5% of all primary care alerts) had a stage 2 or 3 alert, but were not admitted to hospital. Of these 12 patients only 1 had a follow up serum Creatinine level within 30 days.

24.6% (n=152) of all CA-AKI had a measurement of renal function during the 30-day period prior to the AKI alert. Of these 74.3% (n=113) had a blood test in a hospital setting, either as an in-patient (36.2%, n=55), following review at A&E (19.7%, n=30)

or in out-patients 18.4% (n=28). Of the remainder the majority on measurements of renal function were requested in primary care (15.1% n=26).

Significance of Recurrent AKI episodes

The majority of patients (84.7%) generated only one AKI alert. Of those triggering multiple alerts (n=297), 9.8% (n=190) generated 2 alerts, 2.6% (n=26) 3 alerts and 2.9% (n=57) ≥4 alerts.

There was no difference in age or AKI stage of the incident episode with regards to multiple or singular episodes (Table 7). For surviving patients, non-recovery of renal function following the incident AKI episode was associated with a higher probability of a further AKI episode although this did not reach statistical significance (15.4% vs. 18.4%, p=0.16). Multiple AKI episodes were more likely following an incident HA-AKI episode (73.7% vs. 67.1%, P <0.05).

30-day mortality was higher in patients experiencing more than one AKI episode (11.6% vs. 4.6%, P<0.001). Similarly, mortality censored at 4 years, was significantly higher in the cohort with two or more AKI episodes (Figure 2C). Repeated episodes of AKI were also associated with a lower rate of recovery of renal function (86.7 vs. 94.5%, P<0.001).

Significance of an AKI alert based on a serum creatinine within the reference range

Using upper and lower serum creatinine reference range values for age and sex, 58% of AKI alerts in this paediatric population occurs with a creatinine value within the reference range. There was no difference in age between the two groups (Table 8), but as expected alerts with creatinine values above the reference range included more stage 2 or 3 AKI, than those alerting with a normal creatinine (27.6% vs. 7.9%,

P<0.001). 92 patients experienced AKI stage 2/3 with an alerting serum creatinine within the estimated reference range. An alert with a creatinine above the estimated reference range was more common in HA-AKI compared to CA-AKI (64.1% vs. 35.9%, p<0.01). In the CA-AKI patients, those alerting with a creatinine above the reference range were more likely to be admitted to hospital than those alerting within the estimated normal creatinine range (34.1% vs. 12.4%, p<0.001).

30-day mortality was higher in the abnormal creatinine alert cohort (3.1% vs. 0.9%, P<0.001), similarly mortality censored at 4 years (Figure 2D) was also higher in the abnormal creatinine group (p<0.05). Recovery (in the surviving group) was also lower in patients with an alerting serum creatinine above the reference range (91.2 vs. 96.7%, P<0.001).

For those with follow up data, time to recovery was shorter in those alerting with a creatinine above the reference range (4.0 ± 6.5 vs. 4.2 ± 6.3 days, P<0.01). A follow up measure of renal function within 30 days, was more likely for patients with an alert outside of the reference range (75.5% vs. 51.6%, P<0.001), although it is of note that even in this cohort a significant proportion (24.5%) had no follow up measurement.

Discussion

Acute Kidney Injury (AKI) in children is associated with prolonged hospital stay [1], higher in-patient mortality [2], and a higher incidence of chronic renal dysfunction [3]. Whilst the epidemiology of adult AKI is well described, there are few published manuscripts to date describing paediatric AKI. Publications characterising AKI predominantly rely on hospital coding or a retrospective review of hospital records to identify AKI cases [17-20], resulting in underestimation of the true incidence of AKI.

The reported incidence of AKI also varies depending on its definition. The centralised laboratory based identification and alerting of AKI in Wales, has allowed us to generate a national data set to provide characterisation of the epidemiology of AKI in adults [4-11]. To our knowledge the current manuscript reflects a characterisation of the largest cohort of paediatric, non-neonatal, AKI reported to date.

Our reported incidence of AKI is significantly higher than previously reported in children [2, 21, 22]. This likely reflects the methodological differences with a reliance on coding and a focus on hospitalised cases. As expected for the whole cohort the outcomes following AKI both mortality and non-recovery of renal function are related to the severity of the AKI at presentation. It is of note that a large cohort of patients for whom an AKI alert is transmitted, including patients with stage 2 and stage 3 AKI, had no repeat measure of creatinine. This reflects at least in part the lower number of blood tests undertaken in children compared to adults. A recent report suggests that less than 20% of inpatients have repeated blood tests and measurement of f serum creatinine during an in-patient admission [22]. It is also likely that a lack of repeat measure of creatinine reflects a failure to recognise the significance of the AKI alerts.

Our data demonstrate that, as with adults AKI [10], the incidence of AKI is related to social deprivation. In adults, the impact of social deprivation was in part related to a higher burden of co-morbidities. In contrast, in paediatric populations previous studies in non-renal illnesses suggest that social inequality likely reflect environmental and behavioural influences, such as housing conditions and overcrowding [23, 24], air-pollution [25, 26], poor diet and sedentary behaviour[27-29]. The

majority of cases AKI do not represent intrinsic kidney disease but are there result of other primary illnesses which lead to reduced renal perfusion. It is likely that it is alterations in the patterns of common causes/precipitants of AKI that therefore underpin the associations between socio-economic deprivation and the increased incidence of AKI in children. It is also of note that most children need to rely on adult parents or guardians to access medical care, therefore the factors which influence the association between social deprivation and health in adults may also indirectly contribute to the association between social deprivation and health in children.

Within the population with AKI, mortality is higher for HA-AKI. Whilst children with hospitalized-acquired AKI tended to be younger and boys, without clinical data on the associated diagnoses, any explanation of this remains speculative. In contrast to the higher mortality in the HA-AKI group, recovery of renal function in those patients surviving the AKI episode is better than in CA-AKI. This is similar to our reported findings in the adult population. We postulate that the worse renal outcome in the CA-AKI cohort reflect clinical inactivity and a failure to recognise the importance of the alert. This is supported by the lower numbers of patient with CA-AKI who have a repeat measure of creatinine even following severe AKI, and a longer time to repeat for those who do have a repeat measure than HA-AKI. Previously we have demonstrated that roughly a third of CA-AKI have had a measure of renal function within a hospital setting in the four weeks prior to presentation with CA-AKI [6]. In this paediatric cohort, the data again demonstrates that a significant proportion of AKI labelled as CA-AKI have also been seen and had a measure of their renal function in a hospital setting in the weeks prior to the AKI episode. Although labelled as CA-AKI,

the episode may be related to either the illness precipitating the hospital consultation and measure of renal function or changes made in response to the presenting symptoms. AKI, for at least some of these children, may therefore be predictable and/or avoidable.

Recurrent AKI in adults is associated with poor patient outcome [30], and increased risk of progressive CKD [31]. In an adult population, roughly a third of patients experience at least one AKI recurrence [32]. In this study roughly 15% of children, experience more than one AKI episode. This is significantly less than we have previously reported in an adult cohort and likely reflects the smaller burden of co-morbidity in this younger patient group. In an adult population, we have used the presence of pre-existing CKD as a marker of co-morbidity. Over 40% of adult AKI episodes represent AKI with pre-existing CKD [4]. In contrast less than 5% of the paediatric population have pre-existing CKD. Whilst the incidence of repeated AKI episodes is smaller than in an adult cohort, the impact is similarly associated with higher mortality and worse renal outcomes.

Within our data the vast majority of alerts represent AKI stage 1, and more than half of the AKI alerts were generated with a trigger serum creatinine within the reference range. As expected, clinical outcomes were worse for those patients with an alerting creatinine above the reference range. It is of note that cases of stage 2 and 3 AKI were identified with a creatinine within the reference range. AKI episodes in this group whist having a better outcome, carry significant mortality and non-recovery of renal function. Almost two thirds of CA-AKI related to an alerting creatinine within the reference range. A repeat measure of creatinine was less likely if the triggering serum creatinine was within the reference range, with almost half of these patients

having no follow up measure of renal function. In addition, for those who did have a repeat blood test the time to repeat was significantly longer in the group alerting with a creatinine in the reference range. Previous published data have demonstrated that even small increments of serum creatinine adversely impact clinical outcomes in adults [33-35] and children [36]. Our data however suggest that the significance of increases in serum creatinine when they occur within the reference range, even when highlighted with an AKI alert may not be appreciated, and that this may lead to missed opportunities for early intervention to improve clinical outcomes.

This study is to our knowledge the first national study using an e-alert based system to describe the epidemiology of AKI in children, however its findings should be qualified by its limitations. As the e-alert system is IT driven and is based on biochemical parameters only, as a result there is no clinical detail. As a results we are unable to report on the cause of the AKI episodes nor to determine the level of patient co-morbidity and associated primary diagnoses. In addition, we lack data on the need for RRT, and on the cause of death. The study is also limited as the alert is reliant on a previous measurement of renal function in the previous 365 days. As a result, any patient with no measurement of renal function in the previous 365 days but with presenting with a raised creatinine will not be included. Given that most children never have a serum creatinine checked during their childhood, the pediatric population who has had a serum creatinine checked is likely not reflective of the general pediatric population as a whole. Accordingly, the AKI rate reported is most germane for a population in which for some clinical reason there was thought that renal function needed to be assessed in the recent past. It should also be that serum

creatinine is a suboptimal biomarker for renal function, and that using a creatinine based approach to diagnose AKI depending on normal creatinine ranges for age may have limitations in those children in which there are clinical reasons (for instance myopathies or chronic illness with poor nutrition) may have a substantially lower serum creatinine than normal. Although this is likely to represent a small number of children, it may also result in an underestimation of AKI rates in out study. Furthermore, children with such abnormalities are more likely to be in the population who can earn the AKI label in the reporting system since they are more likely than a general population of healthy children to have a serum creatinine in the preceding year.

In conclusion, the manuscript describes the epidemiology of AKI when identified through an electronic AKI alert. It highlights a higher incidence than previously reported and demonstrates that a large number of patient have no follow up measurement of renal function following an AKI alert. This suggests that the significance of the alert may be missed. This may reflect that a large proportion of electronic alerts reported AKI triggered by a rise in serum creatinine which lie within the normal range. These may therefore be interpreted as being insignificant despite a significant increase from the baseline for the patient, although our data would suggest that they have a significant associated morbidity.

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SG and JH designed the study, collected and analysed the data and produced the figures. JDW, KD, GS and JG interpreted the data and wrote the report. AOP set up the program of work, designed the study, interpreted the data and wrote the report.

Figure legends

Figure 1 (on line only): Algorithm for generating e-alerts for Acute Kidney Injury based on serum creatinine (SCr) changes with time. RV, Reference value, defined as the SCr value with which the index SCr value is compared; D, difference between current and lowest previous result within 48 hours; RI, Population reference interval.

Figure 2: [A] Negative Association between the incidence of AKI and the index of social deprivation. 175 patients with missing postcode data were excluded from analysis. WIMD, Welsh Index of Multiple Deprivation, where decile 1 is the most deprived, and decile 10 is the least deprived. [B] Kaplan Meier survival curves for hospital acquired (HA)-AKI vs. community acquired (CA)-AKI. The index episode was used for patients with multiple episodes of AKI. [C] Kaplan Meier survival curves for patients with a single episode of AKI vs. patients with recurrent episodes of AKI. The index episode was used for patients with multiple episodes of AKI. [D] Kaplan Meier survival curves for patients with episodes generated by an AKI e-alert triggered by a creatinine value within the reference range vs. patients with episodes generated by an AKI e-alert triggered by a creatinine value above the reference range. SCr, Serum Creatinine; RR, reference range. The index episode was used for patients with multiple episodes of AKI.

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Table 1. Staging of AKI

Stage	Serum creatinine
1	1.5 -1.9 times baseline or ≥26μmol/L increase
2	2.0-2.9 times baseline
3	3.0 times baseline or ≥354μmol/L

Table 2. E-alert rules.

Rule	Description	Associated alert
1	>26μmol/L increase in creatinine in previous 48 hours	*Acute Kidney Injury alert: rising creatinine within last 48 hours*
2	>50% increase in creatinine in previous 7 days	*Acute Kidney Injury alert: rising creatinine within last 7 days*
3	>50% increase in creatinine against median result for previous 8-365 days	*Acute Kidney Injury alert – creatinine increase over baseline value*

Table 3. AKI e-alert codes and their corresponding triggers, AKI rules, AKI stages

E-alert code	Trigger	AKI rule	AKI stage
DELTA1	D>26μmol/L and no other rule triggered	1	1
ABS1	C1/RV1>C1/RV2 and C1/RV1≥1.5 and C1>354μmol/L	2	3
ABS2	C1/RV2>C1/RV1 and C1/RV2≥1.5 and C1>354μmol/L	3	3
R1AKI1	C1/RV1>C1/RV2 and C1/RV1≥1.5 and C1/RV1<2.0	2	1
R1AKI2	C1/RV1>C1/RV2 and C1/RV1≥2.0 and C1/RV1<3.0	2	2
R1AKI3	C1/RV1>C1/RV2 and C1/RV1≥3.0	2	3
R2AKI1	C1/RV2>C1/RV1 and C1/RV2≥1.5 and C1/RV2<2.0	3	1
R2AKI2	C1/RV2>C1/RV1 and C1/RV2≥2.0 and C1/RV2<3.0	3	2
R2AKI3	C1/RV2>C1/RV1 and C1/RV2≥3.0	3	3

D, Difference between C1 and lowest previous serum creatinine (SCr) value within 48 hours; C1, Index SCr value (current result entered and authorised on the LIMS); RV1, Reference value 1, lowest SCr value existing within previous 7 days; RV2, Reference value 2, median of SCr values existing within previous 8-365 days.

Table 4: Serum Creatinine reference ranges for age and sex

Age (yrs)	Sex	Lower (µmol/l)	Upper (µmol/l)
0-1	M/F	15.03	37.13
1-4	M/F	16.80	43.32
5-9	M/F	22.98	53.92
10-14	M/F	30.94	76.02
15-17	M	38.90	97.24
15-17	F	38.90	91.94

Source: Wales LIMS (Laboratory Information Management System) Harmonisation Group

Table 5: Characteristics of the paediatric cohort

Variable	Whole cohort	HA	CA	P value HA vs. CA
Number of episodes, n (% of whole cohort)	2472 (100)	1719 (69.5)	753 (30.5)	P<0.001
Number of patients, n (%)	1942 (100)	1323 (68.1)	619 (31.9)	P<0.001
Mean (Median) age ±SD (years)	7.3 (5) ±6.1	6.3 (5) ±5.7	9.4 (10) ±6.3	P<0.001
Male, n (%)	1003 (51.6)	729 (55.1)	724 (44.3)	P<0.001
Pre-existing CKD, n (%)	74 (3.8)	54 (4.1)	20 (3.2)	P=n/s
AKI stage 1, n (%)	1635 (84.2)	1118 (84.5)	517 (83.5)	P=n/s
AKI stage 2, n (%)	238 (12.3)	157 (11.9)	81 (13.1)	P=n/s
AKI stage 3, n (%)	69 (3.6)	48 (3.6)	21 (3.4)	P=n/s
Admitted to hospital, n (%)			137 (22.1)	
Repeat test within 30 days, n (%)	1188 (61.2)	922 (69.7)	266 (43.0)	P<0.001
Mean time to repeat ±SD (days)	2.9 ±5.3	2.7 ±5.0	3.4 ±6.0	P<0.01
30-day mortality, n (%)	33 (1.7)	28 (2.1)	5 (0.8)	P<0.05
30-day recovery, n (%)	1010 (94.0)	795 (95.0)	215 (90.7)	P<0.05
Mean time to 30-day recovery ±SD (days)	4.1 ±6.4	4.0 ±6.2	4.5 ±7.0	P=n/s

1,868 patients (1,281, HA; 587, CA) were included in analysis of the 30-day mortality variable. 1,074 patients (837, HA; 237, CA) were included in analysis of the 30-day recovery variable. HA, hospital acquired AKI; CA, community acquired AKI; CKD, Chronic Kidney Disease. The index episode was used for patients with multiple episodes of AKI.

Table 6: Characteristics of the community acquired AKI paediatric cohort						
Variable	**AE**	**OP**	**GP**	**P value AE vs. OP**	**P value AE vs. GP**	**P value OP vs. GP**
Number of episodes, n (% of CA-AKI)	257 (34.1)	250 (33.2)	141 (18.7)	P=n/s	P<0.001	P<0.001
Number of patients, n (% of CA-AKI)	222 (35.9)	193 (31.2)	127 (20.5)	P=n/s	P<0.001	P<0.001
Mean age ±SD (years)	12.3 ±5.7	6.7 ±5.8	9.7 ±6.0	P<0.001	P<0.001	P<0.001

AKI stage 1, n (%)	170 (76.6)	166 (86.0)	115 (90.6)	P<0.05	P<0.01	P=n/s
AKI stage 2/3, n (%)	52 (23.4)	27 (14.0)	12 (9.5)	P<0.05	P<0.01	P=n/s
30-day mortality, n (%)	4 (1.9)	0 (0.0)	0 (0.0)	P=n/s	P=n/s	
30-day recovery, n (%)	116 (88.6)	56 (93.3)	22 (91.7)	P=n/s	P=n/s	P=n/s
Mean time to 30-day recovery ±SD (days)	2.6 ±5.3	5.3 ±7.8	9.7 ±7.1	P<0.001	P<0.001	P=n/s
Repeat test within 30 days, n (%)	147 (66.2)	62 (32.1)	27 (21.3)	P<0.001	P<0.001	P<0.05
Average time to repeat ±SD (days)	1.9 ±5.1	4.5 ±7.0	7.6 ±5.9	7.92E-07	P<0.001	P=n/s
Admitted to hospital, n (%)	90 (40.5)	27 (14.0)	9 (7.1)	P<0.001	P<0.001	P=n/s
Admitted stage 1, n (%)	61 (35.9)	20 (12.1)	9 (7.8)	P<0.001	P<0.001	P=n/s
Admitted stage 2/3, n (%)	29 (55.8)	7 (25.9)	0 (0.0)	P<0.05	P<0.001	P=n/s
Repeat test within 30 days for admitted stage 2/3, n (%)	41 (78.9)	12 (44.4)	1 (8.3)	P<0.01	P<0.001	P<0.05
522 patients (207, AE; 191, OP; 124, GP) were included in analysis of the 30-day mortality variable. 215 patients (131, AE; 60, OP; 24, GP) were included in analysis of the 30-day recovery variable. AE, Accident & Emergency; OP, Out Patient; GP, General Practice. The index episode was used for patients with multiple episodes of AKI.						

Table 7: Characteristics of patients who had a single episode of AKI vs. patients who had recurrent episodes of AKI

Variable	One episode	Recurrent episodes	P value
Number of patients, n (% of whole cohort)	1645 (84.7)	297 (15.3)	
Mean (Median) age ±SD (years)	7.4 (6) ±6.1	6.7 (5) ±5.1	P=n/s
AKI stage 1, n (%)	1391 (84.1)	244 (82.2)	P=n/s
AKI stage 2/3, n (%)	254 (15.4)	53 (17.9)	P=n/s
Hospital acquired, n (%)	1104 (67.1)	219 (73.7)	P<0.05*
Community acquired, n (%)	541 (32.9)	78 (26.3)	P<0.05*
Overall mortality, n (%)	73 (4.6)	33 (11.6)	P<0.001
Overall recovery, n (%)	807 (94.5)	183 (86.7)	P<0.001
Mean time to overall recovery ±SD (days)	3.8 ±5.9	5.4 ±8.0	P<0.001
Repeat test within 30 days, n (%)	950 (57.8)	238 (80.1)	P<0.001
Mean time to repeat ±SD (days)	2.6 ±4.8	3.9 ±6.8	P<0.001
Mean number of episodes ±SD (range)		2.8 ±1.4 (2-11)	

*1,868 patients (1,583, One episode; 285, Recurrent episodes) were included in analysis of the overall mortality variable. 1,065 patients (854, One episode; 211, Recurrent episodes) were included in analysis of the overall recovery variable. *P value is for comparison of hospital acquired vs. community acquired for the 'Recurrent episodes' group. The index episode was used for patients with multiple episodes of AKI.*

Table 8: Characteristics of episodes generated by an AKI e-alert triggered by a creatinine value within the reference range vs. episodes generated by an AKI e-alert triggered by a creatinine value above the reference range

Variable	**Alert SCr in RR**	**Alert SCr above RR**	**P value**
Number of episodes, n (% of whole cohort)	1441 (58.3)	1031 (41.7)	P<0.001
Number of patients, n (% of whole cohort)	1164 (59.9)	778 (40.1)	P<0.001
Mean (Median) age ±SD (years)	6.6 (5) ±6.1	8.3 (7) ±6.0	P<0.001
AKI stage 1, n (%)	1072 (92.1)	563 (72.4)	P<0.001
AKI stage 2/3, n (%)	92 (7.9)	215 (27.6)	P<0.001
Hospital acquired, n (%)	824 (70.8)	499 (64.1)	P<0.01*
Community acquired, n (%)	340 (29.2)	279 (35.9)	P<0.01*
30-day mortality, n (%)	10 (0.9)	23 (3.1)	P<0.001
30-day recovery, n (%)	532 (96.7)	478 (91.2)	P<0.001
Mean time to 30-day recovery ±SD (days)	4.2 ±6.3	4.0 ±6.5	P<0.01
Repeat test within 30 days, n (%)	601 (51.6)	587 (75.5)	P<0.001
Mean time to repeat ±SD (days)	3.4 ±5.7	2.3 ±4.8	P<0.001

*1,868 patients (1,128, Alert SCr in reference range; 740, Alert SCr above reference range) were included in analysis of the 30-day mortality variable. 1,074 patients (550, Alert SCr in reference range; 524, Alert SCr above reference range) were included in analysis of the 30-day recovery variable. SCr, Serum Creatinine; RR, Reference range. *P value is for comparison of hospital acquired vs. community acquired for both groups. The index episode was used for patients with multiple episodes of AKI.*

Figure 1

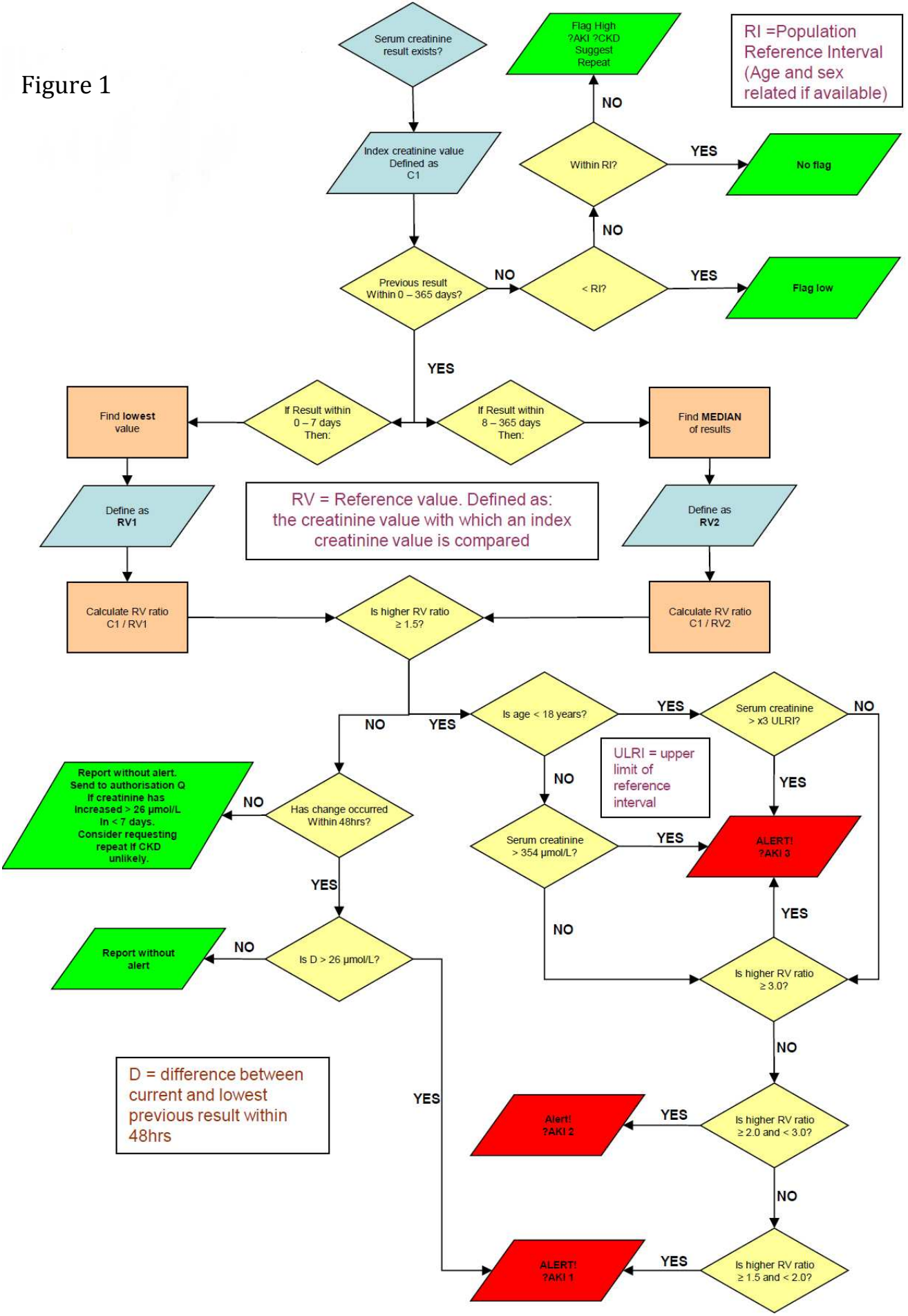
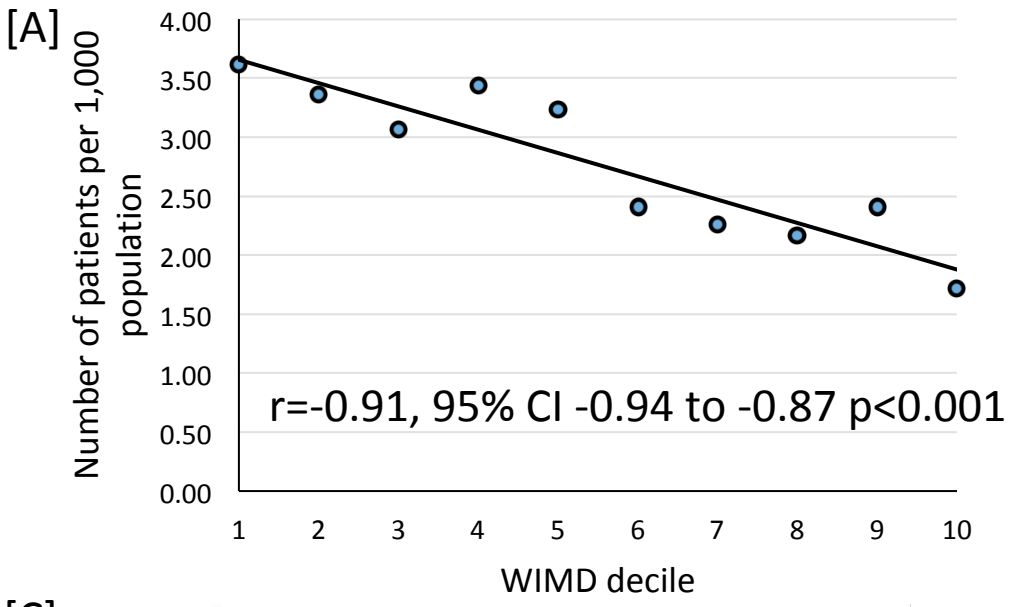
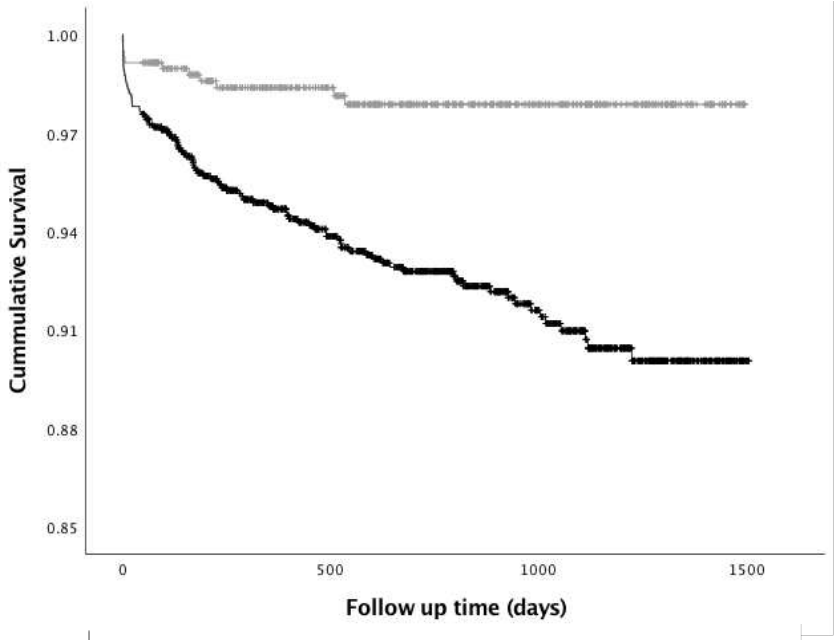
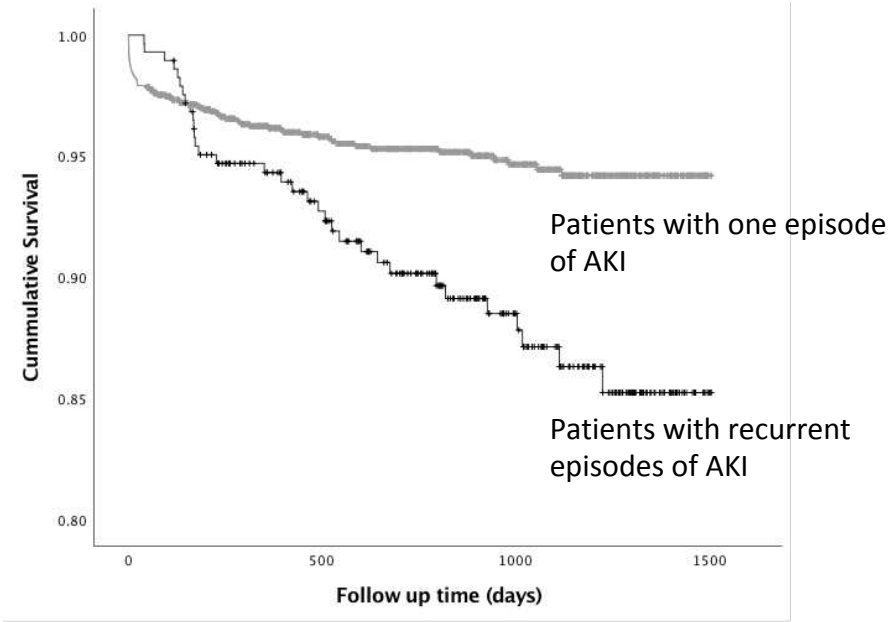
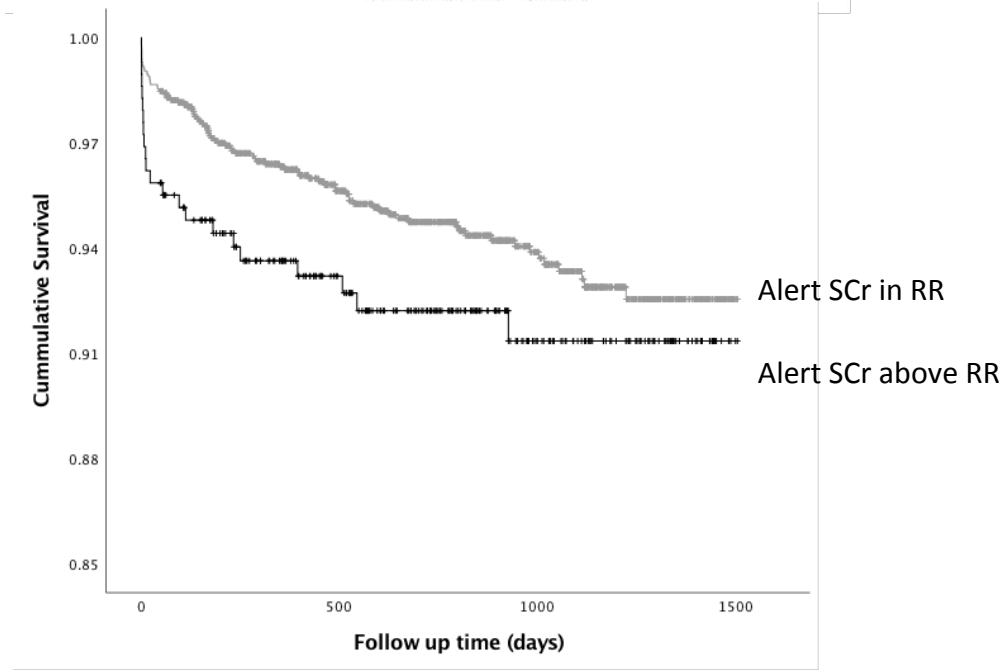

Serum creatinine result exists?
Flag High ?AKI ?CKD Suggest Repeat
RI =Population Reference Interval (Age and sex related if available)
NO
Index creatinine value Defined as C1
Within RI?
YES
No flag
NO
Previous result Within 0 – 365 days?
NO
< RI?
YES
Flag low
YES
Find lowest value
If Result within 0 – 7 days Then:
If Result within 8 – 365 days Then:
Find MEDIAN of results
Define as RV1
RV = Reference value. Defined as: the creatinine value with which an index creatinine value is compared
Define as RV2
Calculate RV ratio C1 / RV1
Is higher RV ratio ≥ 1.5?
Calculate RV ratio C1 / RV2
NO
YES
Is age < 18 years?
YES
Serum creatinine > x3 ULRI?
NO
ULRI = upper limit of reference interval
NO
YES
Report without alert. Send to authorisation Q If creatinine has increased > 26 µmol/L In < 7 days. Consider requesting repeat if CKD unlikely.
NO
Has change occurred Within 48hrs?
Serum creatinine > 354 µmol/L?
YES
ALERT! ?AKI 3
YES
NO
YES
Report without alert
NO
Is D > 26 µmol/L?
NO
Is higher RV ratio ≥ 3.0?
D = difference between current and lowest previous result within 48hrs
YES
NO
Alert! ?AKI 2
YES
Is higher RV ratio ≥ 2.0 and < 3.0?
NO
ALERT! ?AKI 1
YES
Is higher RV ratio ≥ 1.5 and < 2.0?

Figure 2


[A]
Number of patients per 1,000 population
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
r=-0.91, 95% CI -0.94 to -0.87 p<0.001
1
2
3
4
5
6
7
8
9
10
WIMD decile


[B]
Cummulative Survival
1.00
0.97
0.94
0.91
0.88
0.85
0
500
1000
1500
Follow up time (days)


[C]
Cummulative Survival
1.00
0.95
0.90
0.85
0.80
Patients with one episode of AKI
Patients with recurrent episodes of AKI
0
500
1000
1500
Follow up time (days)


[D]
Cummulative Survival
1.00
0.97
0.94
0.91
0.88
0.85
Alert SCr in RR
Alert SCr above RR
0
500
1000
1500
Follow up time (days)