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Utility of electronic AKI alerts in intensive care: A national multicentre cohort study

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Utility of electronic AKI alerts in Intensive Care: A national multicentre cohort study.

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Background: Electronic AKI alerts highlight changes in serum creatinine compared to the patient's own baseline. Our aim was to identify all AKI alerts and describe the relationship between electronic AKI alerts and outcome for AKI treated in the Intensive Care Unit (ICU) in a national multicentre cohort.

Methods: A prospective cohort study was undertaken between November 2013 and April 2016, collecting data on electronic AKI alerts issued.

Results: 10% of 47,090 incident AKI alerts were associated with ICU admission. 90-day mortality was 38.2%. Within the ICU cohort 48.8% alerted in ICU. 51.2% were transferred to ICU within 7 days of the alert, of which 37.8% alerted in a hospital setting (HA-AKI) and 62.2% in a community setting (CA-AKI). Mortality was higher in patients transferred to ICU following the alert compared to those who had an incident alert on the ICU ($p<0.001$), and was higher in HA-AKI (45.3%) compared to CA-AKI (39.5%) (35.0%, $p=0.01$). In the surviving patients, the proportion of patient recovering renal function following, was significantly higher in HA-AKI alerting (84.2%, $p=0.004$) and CA-AKI alerting patients (87.6%, $p<0.001$) compared to patients alerting on the ICU (78.3%).

Conclusion: Using AKI e-alerts provides a centralised resource which does not rely on clinical diagnosis of AKI or coding, resulting in a robust data set which can be used to define the incidence and outcome of AKI in the ICU setting.

Key Words

Acute kidney injury, AKI, electronic alerts, Intensive care, ICU

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Background

Acute Kidney injury (AKI) is a common complication in seriously ill patients which is associated with significant morbidity and mortality. AKI in the Intensive Care Unit (ICU) has different pathophysiological mechanisms and outcomes compared to AKI in a non-ICU population. Many previously published studies characterising AKI in ICU rely on clinical diagnosis, hospital coding or retrospective review of hospital records to identify cases (1-4).

In 2009, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) (5) report identified significant deficiencies in the management of AKI in hospitals in the U.K. This led to the development and implementation of strategies such as the use of electronic results reporting to aid early AKI recognition (6) although to date there is no evidence that implementation of this strategy improved clinical outcome (7). An automated real time electronic (e)-alert for detection of AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) change in creatinine diagnostic criteria has been agreed and implemented nationally across all areas of the National Health Service in Wales and England (U.K.) (8). This automatically compares measured serum creatinine (SCr) values on an individual patient against previous results on the system database. The use of a patient's own historical creatinine data although providing and accurate baseline estimation of renal function does not meet the strict diagnostic criteria for AKI requiring an acute rise within 48hours. In order to understand the possible implication of an AKI e-alert in the context of the ICU, in the current manuscript we have therefore used our centralised system of national data collection and a creatinine based AKI alerts to describe the relationship between electronic AKI alerts, ICU admission and outcome.

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Methods

Setting: Data were collected across the National Health Service in Wales, serving a total adult population of 2.5 million. The study was approved under "Service Evaluation Project Registration".

Development of Electronic Reporting System: The previously described Welsh electronic AKI reporting system (9), utilizes an algorithm based on changes in serum creatinine level (Supplementary Figure 1). AKI is identified by automatically comparing measured creatinine values from an individual patient against previous results in real time. Three "rules" are applied to generate alerts differing in the time period from which the baseline creatinine is obtained. Rule 1 alerts represent a >26μmol/l increase in SCr within the previous 48 hours and are issued only if rule 2 and rule 3 are not satisfied. Rule 2 alerts represent a ≥50% increase in SCr within the previous 7 days, and a rule 3 alert represents a ≥50% increase in SCr from the median of results from the previous 8 to 365 days (8).

Data Collection: Data were collected for all cases of adult (≥18yrs of age) AKI in Wales between November 2013 and April 2016. An incident episode was defined as 90 days. For each episode the clinical location, patient age, AKI stage and the rule under which the AKI alert was generated was collected together with all measurements of renal function for up to 90 days following the AKI alert. To be included in the ICU cohort patients had to have either alerted in ICU, or be transferred to ICU within 7 days of the alert.

Patients with an e-alert generated during a hospital admission with a baseline SCr from a hospital setting within the preceding seven days were defined as Hospital-acquired (HA)-AKI. Patients alerting in a non-inpatient setting (including Accident and Emergency/Acute assessment units) or in primary care were classified as community-

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acquired (CA)-AKI. Patients in whom alerts were generated in an inpatient setting but with no results available for the previous 7 days were excluded from the CA- and HA-AKI subgroup analyses. Progression of AKI was defined as a peak AKI stage higher than the incident e-alert or for stage 3 alerts an increase ≥50% from the SCr generating the alert.

Mortality data were collected from the Welsh Demographic Service. Patients were censored at 27 months for survival analysis. Renal outcome analysis required patients to have 90 day follow up data. Non-recovery was defined as a SCr value measured at 90 days still consistent with AKI when compared to original baseline. Pre-existing chronic kidney disease (PeCKD) was defined as an eGFR (CKDEpi eGFR (15)) <60ml/min/1.73m^2 derived from the baseline SCr.

Statistical analysis was carried out using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student's t test was used for normally distributed data. Categorical data were compared using a Pearson chi-squared test. Multivariate Cox proportional hazard modelling was used to analyse outcome.

Results

We observed a total of 146,512 alerts, representing 47,090 incident AKI alerts. 10.0% of all episodes were associated with ICU admission. Demographic data on AKI episodes requiring ICU are shown in Table 1. Ninety-day mortality was 38.2%. Analysis of the surviving cohort demonstrated recovery from the acute episode occurred in 82.3% of all incident ICU alerts.

Comparison of AKI alerts generated in the community, in a hospital in-patient setting and on the ICU.

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Demographic data on all AKI incident alerts requiring ICU by cohort are shown in Table 3. Of all patients with an e-alert requiring ICU, 2,318 (48.8%) alerted in ICU. 2,428 (51.2%) were transferred to ICU within 7 days of the alert of which 37.8% alerted in a hospital setting and 62.2% in a community setting. Although classified as CA-AKI it is of note that 23.9% of these patient had a measurement of renal function as an inpatient in the preceding 9.8±8.6days, and 20.1% had a measurement of renal function in an A&E setting in the preceding 4.9±6.9days.

AKI severity as determined by the AKI stage of the incident alert was significantly worse for CA-AKI alerts followed by HA-AKI and AKI alerting in ICU. The proportion of patient presenting with a AKI stage 2/3 alerts at presentation was 15.5% in patients alerting on the ICU, 25.1% in HA-AKI alerting patients and 47.8% CA-AKI alerting patients ($p<0.001$).

CA-AKI alerting patients were least likely to experience deterioration of renal function following its initial identification by alert, and HA-AKI alerting patients most likely ($p<0.001$).

Mortality was significantly higher in patients transferred to ICU (41.7%) following the alert compared to those who had an incident alert on the ICU (35%, $p<0.001$), and was significantly higher in HA-AKI (45.3%) alerting patients compared to CA-AKI (39.5%) alerting patients transferred to ICU ($p=0.01$). Higher hazard of death was associated with older age (HR, 1.019; 95% CI, 1.016-1.023; $p<0.001$) and more severe AKI at presentation (AKI 2/3 versus AKI; HR, 1.27; 95% CI, 1.15-1.40; $p<0.001$). Adjusted for these variables the HR of death was higher in patients transferred to ICU following the alert compared to those who had an incident alert on the ICU (adjusted HR, 1.22; 95% CI, 1.12-1.34; $p<0.001$).

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In contrast to mortality, in the surviving patients, the proportion of patients recovering renal function (i.e. death censored renal survival) following an AKI episode, was significantly higher in HA-AKI alerting (84.2%, p=0.004) and CA-AKI alerting patients (87.6%, p<0.001) compared to patients alerting on the ICU (78.3%).

Definitional e-alerts "rules" and ICU.

Table 2 compares the characteristics of the rule 1, rule 2 and rule 3 alerting cohorts. Rule 3, accounted for 45.8%, rule 2 37.3% and rule 1 only 16.8% of all incident alerts. Rule 1 and 2 detected 77.3% of HA-AKI incident alerts whilst 85.2% of CA-AKI incident alerts were detected by rule 3. Rule 3 also identified 48.1% of all acute on chronic kidney injury (A-CKI) alerts, although it is of note that the majority of rule 1 alerts represented A-CKI alerts (53.2%). By the definitional rules, rule 1 AKI alerts are all stage 1 AKI. Rule 3 alerts identified a significantly higher proportion of AKI stage 2 and stage 3 than rule 2 (p<0.001), with 57.7% of all AKI stage 2 and 84.3% of all AKI stage 3 being identified by rule 3 alerts.

Reflecting the level of AKI severity, 90-day mortality for AKI treated in ICU was significantly higher for rule 2 (p=0.008) and rule 3 (p<0.001) alerts than rule 1 alerts (mortality was not significantly different for rule 2 and rule 3 alerts). Similarly, the proportion of patients recovering renal function was highest following a rule 1 alert (89.5%, p<0.001 vs. rule 2 and p=0.04).

Discussion

Although it is widely recognised that AKI is commonly associated with serious illness, there is a wide variation in reported incidence in the context of ICU (10-15). There are limited published data describing patterns of AKI in ICU across the whole spectrum of

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injury, with many key studies focused on severe AKI and patients requiring renal replacement therapy (16-18). In some previously published studies the diagnosis of AKI is reliant on a clinical diagnosis, hospital coding or retrospective review of hospital records (1-4). Other studies have used a creatinine based diagnosis of AKI, but in the absence of any creatinine values in the preceding 3 months (accounting for more than half of the patients in some studies) baseline estimations of renal function were made by solving the Modification of Diet in Renal Disease (MDRD) equation (15, 19). In this study we set out to determine if a centralised data set based on electronic AKI e-alerts using the patient's own historical baseline in all cases, provides a reliable method to characterise AKI in the ICU setting.

From our data AKI requiring the services of ICU accounts for 10% of all incident episodes of AKI identified by a biochemistry based e-alert. This finding is consistent with a population-based study in Scotland in which 9.5% of patients with AKI were treated in the ICU (20), and in which a retrospective diagnosis of AKI was defined by a change in creatinine criteria. Our overall mortality was also consistent with previous published data (19), and also confirms the association of higher mortality with AKI severity regardless of the definitional basis of AKI 'staging' (16, 21, 22). This agreement with previous studies using a variety of methods to identify AKI, suggests that using AKI alerts to generate a platform from which the epidemiology of AKI can be built is valid despite the use of baseline data on renal function which is reliant in almost half of cases on a median value of results from the preceding 365 days (rule 3).

It is of note that while increased severity of AKI in the ICU population is associated with increased mortality, for the surviving patients, non recovery of renal function only occurs in a minority of patients. This is also consistent with previously published data suggesting that severity of AKI in the ICU, assessed by changes in creatinine, predicts

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short term patient survival but does not impact longer term renal outcome, which is in contrast to non-ICU populations (23).

It is important to recognise that clinically, AKI in the setting of ICU is likely to represent a diverse patient group. In this study AKI developing in the ICU represents only half of all AKI treated in the ICU. This is consistent with published data by the NEFROINT investigators reporting of AKI incidence in ICU in Italy (15). Our data suggest that patients in which AKI is diagnosed in the ICU and those in which AKI is identified prior to transfer to the ICU either within the hospital or in a community setting represent different cohorts, with differing AKI stages at presentation being associated with different outcomes in each cohort. There was a higher proportion of AKI stage 2 and 3 in those transferred to ICU with AKI, from both in hospital settings and the community, compared to those developing AKI in the ICU. This suggests that AKI outside the ICU is detected later in the course of the AKI episode. Patients once admitted to the ICU are more likely to have routine surveillance of their biochemical parameters which results in early detection of small increments in serum creatinine. These different patterns of presentation are also reflected in different outcomes with a higher mortality in both groups of patients transferred to ICU following AKI identification.

Confidence in the accurate determination of baseline kidney function is important to convince clinicians of the validity and clinical utility of an automated electronic AKI alert. Current agreed AKI definitions such as The Acute Kidney Injury Network definition rely on a rolling 48-hour window of detection for AKI (24). The use of historical baseline values may therefore not be widely accepted by clinicians. Using strict definitions that do not take into account pre-admission biochemical results to alert AKI are however likely to severely underestimate AKI incidence (25), and result in delays in identification of AKI. Concerns have however been raised that the use of

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automated alerts may have unintended consequences related to over-diagnosis leading to overtreatment (26). In this manuscript we have demonstrated that in the context of ICU treated AKI identified by an electronic alert, Rule 3 alerts generated by rises in creatinine from the median of results from the previous 8 to 365 days, which therefore does not conform to the strict definition of AKI, generates the largest cohort of electronic alerts, the highest proportion of stage 2 and 3 AKI, and 85% of all AKI which develops in the community. Furthermore this rule, representing the furthest "departure" from the strict definition of AKI has the highest mortality reflecting the higher AKI severity. Suppression of this rule therefore would lead to a missed opportunity of AKI in patients presenting at the hospital front door requiring ICU support, which may therefore lead to missed opportunities for early intervention to influence outcome. The current electronic AKI alerting system with its three "rules" highlights high risk patients who require additional clinical scrutiny.

Although this study is to our knowledge the first national study using an e-alert based system to characterise AKI in the ICU its findings need to be qualified by its limitations. Whilst using the centralised data collection simplifies data collection and reduces the burden on busy clinicians, it precludes inclusion of clinical information, such as patient co-morbidity and linkage to primary care data sets, and lacks the detail of the cause of AKI and does not shed light on the cause of death. As a result, we are unable to collect data related to clinical variables which influence both AKI pathophysiology of AKI and outcome. We are unable to report on the initiation of Renal Replacement Therapy (RRT), which impacts on the interpretation on progression of AKI stage as early initiation of RRT to manage fluid balance may result in reductions/stabilisation of creatinine resultant from RRT. Our definition of AKI whilst based on serial changes in serum creatinine does not take into account urine output based AKI diagnosis which

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results in under-reporting of the true incidence of AKI (13, 27). It should also be acknowledged that using recovery of renal function based on serum creatinine may lead to an overestimation of renal function in the critically ill as a result of muscle wasting (28). Finally, outcome data is limited to 90 days. Longer term follow-up is therefore needed to describe the association with progressive CKD. The strengths of the study are the use of a large national data set which uses electronic alerts in which AKI diagnosis is based on the patients' previous test results, providing a unique and contemporary view of AKI across a whole population, and the inclusion of the whole spectrum of AKI disease severity. Moreover, this multicentre study covers the whole of the adult population of Wales therefore avoiding any bias of centre selection. The study demonstrates that using AKI e-alerts provides an opportunity to prospectively collect data using a centralised resource which does not rely on either clinical diagnosis of AKI nor coding data. This approach therefore provides a mechanism to generate a comprehensive data set to define the incidence and outcome of AKI in the ICU setting.

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Acknowledgements: JH designed the study, collected and analysed the data and produced the figures. GR designed the study and validated the algorithm. JG and AD facilitated data collection. NMS, AL, GS and JDW designed the study, interpreted the data and wrote the report. AOP set up the program of work, designed the study, interpreted the data and wrote the report.
The work was carried out under the auspices of the Welsh AKI steering group which is sponsored by the Welsh Renal Clinical Network and Welsh Government

Disclosures; There are no competing interests

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Table 1. Characteristics of AKI episodes requiring the Intensive Care Unit (ICU).

Variable	**ICU**
n (% of all incident alerts)	4746 (10.0)
Mean age ±SD (yr)	66.4 ±15.0
Sex	
Male	58.7 (2786)
Female	41.2 (1960)
Pre-existing CKD, % (n)	28.0 (1321)
Mean baseline SCr ±SD (µmol/L)	88.6 ±48.2
Mean baseline eGFR ±SD (ml/min/1.73m^2)	78.4 ±30.4
Mean alert SCr ±SD (µmol/L)	182.1 ±146.7
AKI Severity, % (n)	
Stage 1	70.3 (3337)
Stage 2	17.2 (816)
Stage 3	12.5 (593)
Progression of AKI, % (n)	38.5 (1829)
Mean peak SCr±SD(µmol/L)	240.6 ±180.4
90-day mortality, % (n)	38.1 (1664)
Renal Recovery, % (n)	82.3 (2512)

Baseline eGFR data were missing for 35 episodes) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 4362 episodes. SCr follow up data was available for 3053 episodes) and included in analysis of the recovery variable. PeCKD, Pre-existing chronic kidney disease; SCr, Serum creatinine; ICU, Intensive Care Unit.

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Table 2. Comparison of patients whose AKI was identified in ICU vs. HA-AKI patients transferred to ICU following an AKI e-alert vs. CA-AKI patients transferred to ICU following an AKI e-alert.

Variable	AKI identified in ICU	HA-AKI transferred to ICU	CA-AKI transferred to ICU	
n (% of episodes requiring ICU)	2318 (48.8)	835 (17.6)	1373 (28.9)	
Mean age ±SD (yr)	66.9 ±14.6	68.3 ±14.5	64.2 ±15.8	
Sex				
Male	61.2 (1419)	58.1 (485)	55.6 (763)	
Female	38.7 (899)	41.9 (350)	44.4 (610)	
Pre-existing CKD, % (n)	26.0 (598)	30.1 (250)	29.5 (404)	
Mean baseline SCr ±SD (μmol/L)	86.0 ±48.7	88.3 ±46.4	92.6 ±49.4	
Mean alert SCr ±SD (μmol/L)	144.9 ±77.8	160.6 ±83.4	245.2 ±207.0	
AKI Severity, % (n)				
Stage 1	82.1 (1902)	73.4 (613) *	52.0 (714) * #	*P<0.001 vs. in ICU #p<0.001 vs. HA-AKI
Stage 2	13.6 (315)	18.0 (150)*	21.7 (298)) * #	
Stage 3	4.4 (101)	8.6 (72)*	26.3 (361)) * #	
AKI Rule, % (n)				
Rule 1	25.8 (599)	17.5 (146)	3.7 (51)	
Rule 2	51.3 (1189)	50.5 (422)	11.1 (152)	
Rule 3	22.9 (530)	32.0 (267)	85.2 (1170)	
Progression of AKI, % (n)	41.0 (951)	49.1 (410) *	28.7 (394)) *#	*P<0.001 vs. in ICU #p<0.001 vs. HA-AKI
Mean peak SCr±SD(μmol/L)	204.5 ±139.2	234.3 ±142.1	294.2 ±226.8	
90-day mortality, % (n)	35.0 (763)	45.3 (343)*	39.5 (484) †#	*P<0.001 vs. in-ICU †p=0.009 vs. in-ICU #p=0.01 vs. HA-AKI
Recovery, % (n)	78.3 (1204)	84.2 (410)*	87.6 (775)*	*P<0.001 vs. in ICU

Baseline eGFR data were missing for 35 episodes (24, AKI identified in ICU; 5, HA-AKI transferred to ICU; 4, CA-AKI transferred to ICU) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 4362 episodes (2177, AKI identified in ICU; 757, HA-AKI transferred to ICU; 1225, CA-AKI transferred to ICU). SCr follow up data was available for 3053 episodes (1538, AKI identified in ICU; 487, HA-AKI transferred to ICU; 885, CA-AKI transferred to ICU) and included in analysis of the Recovery variable. HA-AKI, Hospital acquired AKI; CA-AKI, Community acquired AKI; PeCKD, Pre-existing chronic kidney disease; SCr, Serum creatinine; ICU, Intensive Care Unit.

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Table 3. Characteristics and outcomes for the Rule 1, Rule 2 and Rule 3 cohorts for AKI episodes treated on the Intensive Care Unit (ICU).

	Rule 1	**Rule 2**	**Rule 3**	
n (% of ITU cohort)	798 (16.8)	1772 (37.3)	2176 (45.8)	
Mean age ±SD (yr)	70.1 ±14.0	66.0 ±15.9	65.2 ±15.4	
Sex, % of ICU cohort (n)				
Male	69.0 (551)	55.3 (980)	57.7 (1255)	
Female	31.0 (247)	44.7 (792)	42.3 (921)	
Pre-existing CKD, % (n)	53.2 (413)	15.4 (272)	29.3 (636)	
Mean baseline SCr ±SD (µmol/l)	122.0 ±58.0	69.1 ±30.7	92.4 ±48.5	
Mean alert SCr ±SD (µmol/l)	161.7 ±67.3	130.1 ±62.3	231.8 ±193.1	
AKI Severity, % (n)				
Stage 1	100.0 (798)	75.3 (1334)*	55.4 (1205)*#	*P<0.001 vs. rule 1 #p<0.001 vs. rule 2
Stage 2		19.5 (345)*	21.6 (471)*#	
Stage 3		5.2 (93)*	23.0 (500)*#	
ICU classification, % (n)				
AKI identified in ICU	75.1 (599)	67.1 (1189)	24.4 (530)	
HA-AKI transferred to ICU	18.3 (146)	23.8 (422)	12.3 (267)	
CA-AKI transferred to ICU	6.4 (51)	8.6 (152)	53.8 (1170)	
Progression of AKI, % (n)	32.6 (260)	47.2 (836)*	33.7 (733)	*p=0.008 vs. rule1 and rule 3
Mean peak SCr ±SD (µmol/l)	227.3 ±130.9	190.8 ±134.1	286.1 ±214.4	
90-day mortality, % (n)	32.5 (244)	38.2 (628)*	40.3 (792)#	*p=0.008 vs. rule1 #p<0.001 vs. rule 1
Recovery, % (n)	89.5 (485)	74.2 (1136)*	86.1 (1184)#†	*p<0.001vs rule1 #p=0.04 vs. rule 1 †p=<0.001 vs. rule 2

Baseline eGFR data were missing for 25 episodes (11, Rule 1; 8, Rule 2; 6, Rule 3) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 4362 episodes (750, Rule 1; 1646, Rule 2; 1966, Rule 3). SCr follow up data was available for 3053 episodes (542, Rule 1; 1136, Rule 2; 1375, Rule 3) and included in analysis of the recovery variable. 220 incident episodes of AKI were excluded from analysis of the ICU classification variable as it was not possible to classify as HA/CA or ICU AK. I HA-AKI, Hospital acquired AKI; CA-AKI, Community acquired AKI; PeCKD, Pre-existing chronic kidney disease; SCr, Serum creatinine; ICU, Intensive Care Unit.

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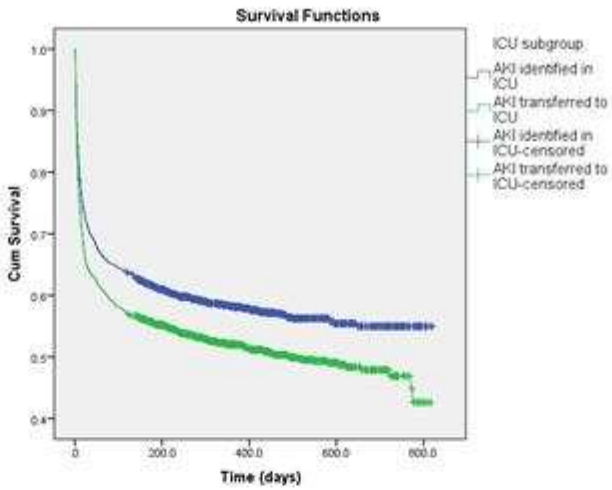
Figure 1

A



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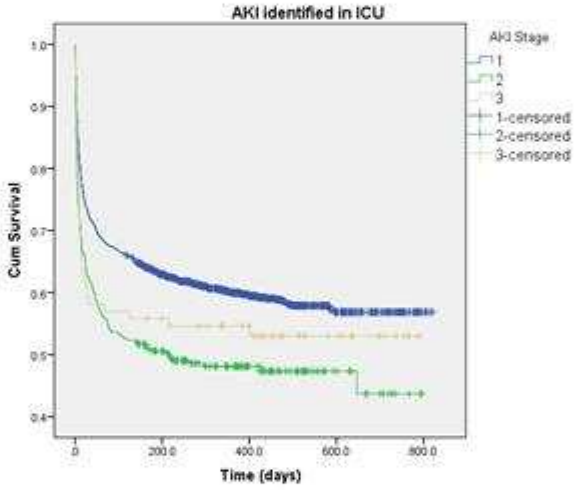

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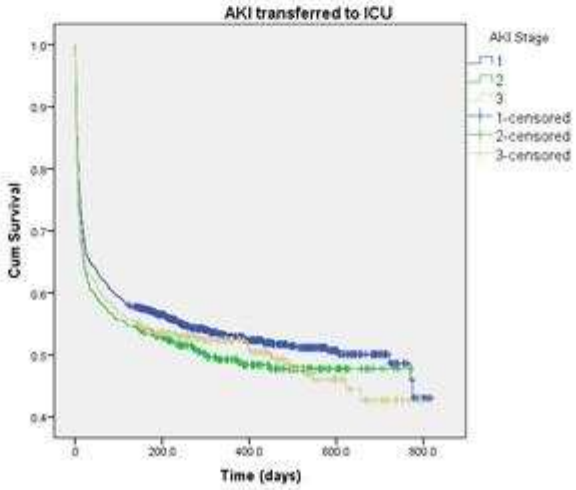

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Highlights

- Data on epidemiology of AKI historically is reliant on coding or retrospective clinical diagnosis
- We describe the epidemiology of AKI in the ICU based an electronic AKI alert based on a change in creatinine diagnosis of AKI

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