Understanding Electronic AKI Alerts: Characterization by definitional rules

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Introduction: Automated acute kidney injury (AKI) electronic alerts are based on comparing creatinine with historic results.

Methods: We report the significance of AKI defined by 3 “rules” differing in the time period from which the baseline creatinine is obtained, and AKI with creatinine within the normal range.

Results: A total of 47,090 incident episodes of AKI occurred between November 2013 and April 2016. Rule 1 (>26 \(\mu\)mol/l increase in creatinine within 48 hours) accounted for 9.6%. Rule 2 (>50% increase in creatinine within previous 7 days) and rule 3 (>50% creatinine increase from the median value of results within the last 8–365 days) accounted for 27.3% and 63.1%, respectively. Hospital-acquired AKI was predominantly identified by rules 1 and 2 (71.7%), and community-acquired AKI (86.3%) by rule 3. Stages 2 and 3 were detected by rules 2 and 3. Ninety-day mortality was higher in AKI rule 2 (32.4%) than rule 1 (28.3%, \(P<0.001\)) and rule 3 (26.6%, \(P<0.001\)). Nonrecovery of renal function (90 days) was lower for rule 1 (7.9%) than rule 2 (22.4%, \(P<0.001\)) and rule 3 (16.5%, \(P<0.001\)). We found that 19.2% of AKI occurred with creatinine values within normal range, in which mortality was lower than that in AKI detected by a creatinine value outside the reference range (22.6% vs. 29.6%, \(P<0.001\)).

Discussion: Rule 1 could only be invoked for stage 1 alerts and was associated with acute on chronic kidney disease acquired in hospital. Rule 2 was also associated with hospital-acquired AKI and had the highest mortality and nonrecovery. Rule 3 was the commonest cause of an alert and was associated with community-acquired AKI.

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KEYWORDS: acute kidney injury; electronic alerts; outcome

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Acute kidney injury (AKI) is a global health issue characterized by an abrupt loss of kidney function that is strongly associated with high mortality and morbidity. The reported incidence of AKI varies depending on its definition, the clinical setting in which it is detected, and the population studied. Based on a presumption that early identification may help raise standards of care and improve patient outcomes, an automated real-time electronic alert (e-alert) system for AKI based on the Kidney Disease: Improving Global Outcomes change in creatinine diagnostic criteria has been established and implemented nationally across all areas of the National Health Service in Wales, and the other home countries of the United Kingdom.

To generate the AKI e-alert, the all-Wales Laboratory Information Management System (InterSystems TrakCare Lab, Cambridge, MA) automatically compares measured serum creatinine (SCr) values in an individual patient against previous results on the system database. Alerts are grouped according to the time frame between the incident blood test and the baseline with which it is compared to generate the alert. Alerts generated using a baseline derived from SCr results taken in the previous 48 hours conform to “rule 1,” 7 days “rule 2,” and those alerts generated using a baseline derived from the median of SCr results from the previous 8–365 days represent “rule 3.” The use of these variable baselines allows a direct patient-specific comparator and avoids the need to generate an estimated baseline for example as derived from estimates, using the Modification of Diet in Renal Disease Study (MDRD) equation assuming a glomerular filtration rate of 75 ml/min per 1.73 m². The use of historic SCr results that may date back many months may potentially generate a
number of false positive AKI cases, which may lead to clinician “alert fatigue” and could undermine the primary purpose of the electronic alerting system. In addition, the process by which automated alerts are issued is such that alerts are transmitted even when SCr values remain within the normal reference range. Although published data suggest that small changes in SCr are associated with adverse outcomes after AKI, it is not clear if this also applies when the changes occur within the normal reference range.

To allow clinicians to further understand the clinical significance of electronic AKI alerts, in the current study, we have examined the significance of the alerts generated by each of the “rules,” in terms of mode of presentation, severity of injury, and outcome. In addition, we have examined the significance of alerts generated by SCr values that satisfy the definition of AKI based on the change in SCr over baseline, but occur within the normal population reference range.

**METHODS**

**Setting**

Data were collected across the National Health Service in Wales that serves a population of 3.06 million. The study was approved under “Service Evaluation Project Registration.”

**Development of an Electronic Reporting System**

The previously described (and validated) Welsh electronic AKI reporting system utilizes the all-Wales Laboratory Information Management System (InterSystems TrakCare Lab), which in real time automatically compares measured creatinine values in an individual patient against previous results, to generate alerts using an algorithm based on changes in SCr level (Supplementary Figure S1). AKI is identified by automatically comparing measured SCr values from an individual patient against the previous available results in real time, generating alerts based on Kidney Disease: Improving Global Outcomes AKI staging criteria. Three “rules” are applied to generate alerts differing in the time period from which the baseline creatinine is obtained. Each e-alert rule together with the comment that accompanies the e-alert is shown in Table 1. Rule 1 alerts represent a >26 μmol/l increase in SCr within the previous 48 hours and are issued only if rules 2 and 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.

**Data Collection**

Prospective data were collected for all cases of adult (≥18 years of age) AKI in Wales between November 2013 and April 2016. Details of cohort creation are shown in Figure 1. We defined an incident episode of AKI as 90 days, that is, any AKI e-alert for the same patient within 90 days of the incident alert was not considered a new episode. Any alerts outside the 90-day window were defined as a new event. For each episode, patient age, AKI stage, and the rule under which the AKI alert was generated were collected together with all measurements of renal function for up to 90 days after the AKI alert.

Patients with an e-alert generated during a hospital admission with a baseline SCr generated in hospital within the preceding 7 days were defined as hospital-acquired (HA)-AKI. Patients with an e-alert generated in a noninpatient setting (including accident and emergency/acute assessment units) or in primary care were classified as community-acquired (CA)-AKI. To be classified as AKI treated in an intensive care unit (ICU) patients either alerted in the ICU, or had a measurement of renal function in the ICU within 7 days of the alert. Peak AKI stage was assigned by comparing the highest SCr value reached during an incident episode with the baseline SCr of the incident alert. Progression of AKI was defined as a peak AKI stage higher than the stage associated with the incident e-alert or for stage 3 alerts with an increase of ≥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 available. Nonrecovery was defined as achievement of an SCr value measured closest to and within 90 days still in keeping with AKI when compared with baseline.

Pre-existing chronic kidney disease was defined as an estimated glomerular filtration rate (CKD-Epi eGFR) <60 ml/min per 1.73 m² derived from the baseline SCr. Using the SCr value that generated the alert, we classified the data in relation to SCr population reference ranges and used 58—110 μmol/l for males and 46—92 μmol/l for females. These are currently the reference intervals used across Wales (Wales Laboratory Information Management System Harmonisation).

Statistical analysis was carried out using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student’s t-test
test was used for the analysis of normally distributed data. A Mann-Whitney U test was used for the analysis of non-normally distributed data. Categorical data were compared using a Pearson chi-squared test.

RESULTS

Characterization of AKI by "Rules"

We observed a total of 47,090 incident episodes of AKI with follow-up data available. Table 2 compares the characteristics of the rule 1, rule 2, and rule 3 cohorts. The majority (63.1%) of all incident episodes were generated based on rule 3. Rule 1 and rule 2 accounted for 9.6% and 27.3% of all episodes, respectively.

The majority (71.7%) of all HA-AKI were identified by rules 1 and 2. In contrast, the majority of CA-AKI (86.3%) were identified by rule 3. Rule 3 also identified the majority (66.6%) of all acute on chronic kidney injury although it is of note that the majority of rule 1 alerts represented acute on chronic kidney injury (65.0%).

Severity of AKI by Rules

All rule 1 AKI alerts were AKI stage 1, with AKI stages 2 and 3 detected exclusively by rules 2 and 3. There were a higher proportion of rule 3 triggered alerts with AKI stage 2 and AKI stage 3 than rule 2 (AKI stage 2: rule 3, 16.9% vs. rule 2, 14.2%, \( P < 0.001 \); AKI stage 3: rule 3, 11.3% vs. rule 2, 3.3%, \( P < 0.001 \)). Consequently, the majority of AKI stages 2 (73.3%) and 3 (88.9%) were triggered by rule 3.

Progression of AKI to either a higher AKI stage, or in the case of stage 3 a further increase in SCr by \( \geq 50\% \), was greater after a rule 2 incident alert and was comparable for rule 1 and rule 3 alerts. In addition to progression of the AKI stage, we used ICU admission as a marker of “episode severity.” Although the highest proportion of AKI treated in the ICU were in the rule 3 cohort (45.8% of all ICU-treated AKI), within each rule, the proportion of ICU-treated AKI was greater in the rule 1 cohort (17.7%) than the rule 2 cohort (13.8%, \( P < 0.001 \)), which in turn was higher than the rule 3 cohort (7.3%, \( P < 0.001 \)).

The Relationship Between Rules and Outcomes

Ninety-day mortality for all AKI episodes was 28.3%. Mortality was significantly higher in AKI detected by rule 2 compared with that detected by rules 1 and 3.
The proportion of patients who had a recurrent episode of AKI was the same across the 3 rules (Table 2).

**Significance of AKI Within Creatinine Reference Range**

Table 3 compares the characteristics of the patients with AKI and a rise in SCr within the reference range to those with a rise outside the reference range (the Welsh normal reference range for creatinine is 46–92 μmol/l for females and 58–110 μmol/l for males). Alerts generated when a rise in SCr occurred within the normal reference range accounted for 19.2% of all AKI alerts. There was a greater proportion of AKI stage 1 compared with the cohort that alerted with an SCr value outside the reference range (95.4% vs. 73.2%, \( P < 0.001 \)). There was no statistical difference between the 2 groups for progression of AKI (within reference range 23.4%, outside reference range 25.4%, \( P = 0.37 \)), although the proportion of patients who progressed from AKI stage 1 to AKI stage 3 was greater than those in whom the SCr remained within the reference range (43.7% vs. 37.1%, \( P = 0.006 \)). The need for treatment in the ICU was no different between the 2 groups.

Ninety-day mortality for patients with AKI and a rise in SCr within the reference range was 22.6%, which was significantly lower than mortality for patients with AKI detected by an SCr value outside the reference range (29.6%, \( P < 0.001 \)). Mortality was higher for AKI stage 1 for patients with SCr outside the reference range (Figure 3a), but no different for AKI stage 2 between the 2 groups. For those with an alerting SCr within the reference range, patients with AKI stage 2 had higher mortality than those with AKI stage 1 (34.5% vs. 22.1%, \( P < 0.001 \)). The small number of patients with AKI stage 3 detected by an SCr value within the reference range precluded meaningful analysis.

**DISCUSSION**

The National Confidential Enquiry report in 2009 reported that up to 50% of patients with AKI may experience suboptimal care that may subsequently translate into episodes of preventable harm. Given the lack of specific therapy, other than supportive measures, for established AKI, early intervention offers the best opportunity to improve patient outcomes. Any improvement in clinical outcome will therefore be dependent on early detection to trigger prompt re-assessment of patients, close monitoring of patient

![Table 2](https://example.com/table2.png)

|                | Rule 1 | Rule 2 | Rule 3 |
|----------------|--------|--------|--------|
| n (% of incident episodes) | 45.18 (9.6) | 12.849 (27.3) | 29.723 (63.2) |
| Mean age ± SD (yr) | 75.2 ± 14.4 | 72.6 ± 15.9 | 71.5 ± 16.5 |
| Sex, % (n) | | | |
| Male | 62.0 (2800) | 44.6 (5728) | 46.4 (13,777) |
| Female | 38.0 (1716) | 55.4 (7121) | 53.6 (15,944) |
| Pre-existing CKD, % (n) | 65.0 (2901) | 20.7 (2657) | 37.4 (11,097) |
| Mean baseline SCr (μmol/l) | 127.9 | 70.9 | 93.3 |
| Mean baseline eGFR (ml/min per 1.73 m²) | 51.9 | 83.7 | 70.8 |
| Mean alert SCr (μmol/l) | 167.2 | 127.6 | 187.5 |
| Mean peak SCr (μmol/l) | 211.5 | 160.7 | 218.4 |
| Mean nadir eGFR associated with peak SCr (ml/min per 1.73 m²) | 30.5 | 44.8 | 33.9 |
| AKI severity, % (n) | | | |
| Stage 1 | 100.0 (4518) | 82.5 (10,606) | 71.8 (21,340) |
| Stage 2 | 14.2 (1822) | 16.9 (5010) | 16.9 (5010) |
| Stage 3 | 3.3 (421) | 11.3 (3373) | 11.3 (3373) |
| Peak AKI stage, % (n) | | | |
| Stage 1 | 80.2 (3624) | 56.7 (7281) | 55.7 (16,549) |
| Stage 2 | 11.8 (532) | 25.6 (3295) | 23.7 (7046) |
| Stage 3 | 8.0 (362) | 17.7 (2273) | 20.6 (6128) |
| Clinical location, % (n) | | | |
| HA-AKI | 79.3 (3582) | 79.9 (10,269) | 81.4 (2563) |
| CA-AKI | 18.7 (844) | 17.7 (2267) | 19.3 (5756) |
| Undetermined in hospital alerts | 2.0 (92) | 2.4 (313) | 15.6 (4648) |
| Progression of AKI, % (n) | 19.8 (894) | 31.4 (3906) | 22.8 (6018) |
| Requirement of ICU, % (n) | 17.7 (788) | 13.8 (1772) | 7.3 (2176) |
| Repeat AKI episodes, % (n) | 18.2 (541) | 20.5 (1614) | 18.6 (3537) |

Data on patient sex were missing for 4 cases (2, rule 1; 2, rule 3) and excluded from analysis of the sex variable. Baseline eGFR data were missing for 128 cases (57, rule 1; 26, rule 2; 52, rule 3) and excluded from the analysis of the pre-existing CKD variable. AKI, acute kidney injury; HA-AKI, hospital-acquired AKI; CA-AKI, community-acquired AKI; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; ICU, intensive care unit.
physiology, review of medication, or consideration of hospitalization. In response to this, a clinical and automated real-time e-alert system for AKI based on the Kidney Disease: Improving Global Outcomes change in creatinine diagnostic criteria has been established and implemented nationally across all areas of the National Health Service in Wales. A similar approach has also been mandated in NHS England using the same algorithm for defining AKI. Both systems are dependent on satisfying one of 3 criteria based on a change in serum creatinine differing in the time period of creatinine change.

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. The use of historical baseline values may therefore not be widely accepted by clinicians. Using strict definitions

Figure 2. Differing outcomes associated with incident acute kidney injury (AKI) electronic alerts for AKI rules. (a) Ninety-day mortality rates, dividing according to the AKI rule. Mortality data were available for 41,596 patients (4086, rule 1; 11,646, rule 2; 25,864, rule 3). *P < 0.001 rule 2 versus rule 1 and rule 2 versus rule 3. (b) Ninety-day mortality rates, dividing according to the AKI stage and rule. Mortality data were available for 41,596 patients (32,446, stage 1 [4086, rule 1; 9615, rule 2; 18,745, rule 3]; 5955, stage 2 [1664, rule 2; 4291, rule 3]; 3195, stage 3 [367, rule 2; 2828, rule 3]). *P < 0.001 versus rule 1, #P < 0.001 versus rule 3, **P < 0.001 versus AKI1, ##P < 0.001 versus AKI2. (c) Renal outcome of patients with AKI, dividing according to the AKI rule. Renal outcome data were available for 33,512 episodes (3255, rule 1; 8709, rule 2; 21,548, rule 3). #P < 0.001 versus rule 1. (d) Nonrecovery of patients with AKI, dividing according to the AKI stage and AKI rule. Renal outcome data were available for 33,512 episodes (26,470, stage 1 [3255, rule 1; 7331, rule 2; 15,884, rule 3]; 4543, stage 2 [1128, rule 2; 3415, rule 3]; 2499, stage 3 [250, rule 2; 2249, rule 3]). #P < 0.001 rule 2 versus rule 3.
that do not take into account predischARGE biochemical results to generate AKI alerts are, however, likely to severely underestimate AKI incidence, and result in delays in identification of AKI. This may negatively impact the opportunity for early clinical intervention. Numerous studies have demonstrated that alerts have been effective in altering clinicians behavior in various contexts, such as time to respond to laboratory results and medication prescription. Concerns have, however, been raised that the use of automated alerts may have unintended consequences related to over-diagnosis leading to overtreatment. The generation of a large volume of alerts within the clinical environment drives a perception that the alert generates additional work that impedes workflow, leading to “alert fatigue” causing clinicians to over-ride or disregard the alert.

Using a centralized system of national data collection, the electronic alert, and a creatinine-based diagnosis of AKI, we have previously undertaken a comprehensive characterization of the incidence of AKI, and its outcome across both primary and secondary care, in both adult and pediatric patients. These studies reported an incidence of AKI that is far greater than a previously reported incidence in studies reliant on clinical identification of adult AKI or hospital coding data fueling fears that the detection of AKI using an automated alert may overwhelm the busy clinician. In light of a recent study demonstrating that approval of an AKI alert system relies on the clinician’s view of the likely benefit to patient care, and that approval wanes with time, it is important to understand the implication of the alerts generated by the different rules used by the algorithm.

Our data demonstrate that rule 1, as defined by the algorithm, could only be invoked for stage 1 alerts, and was associated with acute on chronic kidney disease acquired in hospital. Previous studies indicate that small absolute increases in creatinine are associated with lower mortality in CKD. Although the absolute increase in creatinine in this study was smallest for rule 1 based AKI, its mortality over 20%. Mortality was highest in rule 1 AKI, and had the highest mortality and nonrecovery.

Figure 3. Mortality associated with incident acute kidney injury (AKI) electronic alerts for reference range classifications according to the AKI stage. Mortality data were available for 41,596 patients (32,446, stage 1 [7714, alerting SCR within RR; 24,732, alerting SCR within RR]; 5955, stage 2 [333, alerting SCR within RR; 5622, alerting SCR within RR]; 3195, stage 3 [24, alerting SCR within RR; 3175, alerting SCR within RR]). #P < 0.001 mortality within RR versus outside RR, *P < 0.001 for AKI2 versus AKI1 within RR only. RR, reference range; SCR, serum creatinine.
differences in the patient characteristics, we speculate that this may be reflective of frequency of measurement of creatinine indicating the severity of the patients’ clinical condition.

Although the use of historical baseline values may be contentious, exclusion of alerts generated using such data would undermine the alerting system as it fails to detect the more severe stages of AKI. Rule 3 alerts, based on an increase in creatinine from the median of results from the previous 8 to 365 days, detect the majority of all AKI, the highest proportion of stage 2 and 3 AKI, and 86% of all AKI that develop in the community. Although numerous studies have described the epidemiology, risk factors, and outcomes for patients developing AKI during hospitalization, less attention has focused on AKI that has developed in the community. Our previous studies suggest that up to half of all AKI are community acquired, with a significant proportion of these patients not being admitted to hospital. CA-AKI represents a group of patients with more severe AKI (by AKI stage) at presentation than HA-AKI, comparable 90-day mortality to HA-AKI for hospitalized patients, and a significant impact on 3-year patient survival. In contrast to CA-AKI, HA-AKI is identified by rule 1 and rule 2 criteria. It is therefore clear that the different rules generating AKI alerts identify different cohorts of patients with AKI, which in part are the product of the algorithm itself. It is however important to note that for all of the patients identified, the incident AKI episode is associated with a significant negative impact with all rules demonstrating a comparable rate of subsequent worsening of renal injury and longer term impact on renal function.

In our study, roughly 20% of all AKI alerts were generated by serum creatinine that was within the normal reference range. Alerts generated within the normal serum creatinine reference range were overwhelmingly stage 1 AKI. Within this group progression to a worse stage of AKI and the need for ICU was no different to the whole cohort. This is consistent with multiple previous studies in numerous clinical settings, which suggest that even small increases in creatinine are associated with adverse clinical outcomes, even when the increase in serum creatinine does not meet AKI criteria.

To receive widespread approval, an alert requires good diagnostic performance with the significance and the context of the alert communicated to the end-user. The data in this paper demonstrate that although the use of an electronic AKI alert highlights a large cohort of patients, the use of historical and current baseline creatinine values identifies different cohorts of patients in whom AKI has a significant impact on clinical outcomes. Although alert fatigue may be avoided by suppression of some alerts to reduce the number of alerts issued, the data also suggest that this would lead to the exclusion of a number of high-risk patients. It should be emphasized that the alert does not suggest diagnostic certainty and needs to be applied to the clinical context. Furthermore, it should be noted that the alert is dependent on availability of previous results. Hence for some patients without baseline SCr data, AKI may only be identified in retrospect, when their biochemistry SCr levels return to reference range. In these patients, diagnosis of AKI requires clinical vigilance that should include evaluation of urine output, an AKI diagnostic criterion beyond the scope of an automated biochemistry-based system. Finally, an automated detection system can only categorize according to its preprogrammed criteria, and therefore for patients with infrequent blood tests, the patients’ full medical history may be needed to help distinguish between AKI and CKD. Despite these limitations and caveats, the current electronic AKI alerting system does highlight high-risk patients who require additional clinical scrutiny, and the data in this paper may go some way to allay skepticism and increase end-user acceptance. Currently however, we have no information to suggest that the issuing of alerts has alerted clinician behavior and more importantly patient outcome.

DISCLOSURE
All the authors declared no competing interests.

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JH designed the study, collected and analyzed the data and produced the figures. GR designed the study and validated the algorithm. SM 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.

SUPPLEMENTARY MATERIAL
Figure S1. Algorithm for generating e-alerts for acute kidney injury based on serum creatinine changes with time. Supplementary material is linked to the online version of the paper at www.kireports.org.
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