# UTILISING ROUTINE POPULATION HEALTHCARE DATA FOR EPIDEMIOLOGICAL RESEARCH AND QUALITY IMPROVEMENT IN CARE: APPLICATION OF A NATIONAL ACUTE KIDNEY INJURY ALERTING SYSTEM AS A PROOF OF CONCEPT

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**Abstract**

Acute kidney injury (AKI) is a global health issue known to cause avoidable harm and death. Improvement in its prevention and management is therefore considered an important goal for the healthcare sector. While improvement science states that without measurement, improvement is not possible, at the outset of this research, the epidemiology of AKI was also not fully understood. Whereas numerous studies had described AKI that is developed during hospitalisation, less had focused on that developed in the community. This healthcare informatics thesis centres on the proposed utilisation of routine serum creatinine (SCr) data for informing both the epidemiology of AKI, and improvement in care for patients who develop and/or are at risk of AKI. It follows the recent implementation of an automated laboratory-based electronic alerting system for AKI across the entire Welsh National Health Service which, in addition to its primary purpose of aiding early intervention, also had potential to be applied as a centralised system of data collection.

The first of three projects documented in the portfolio style thesis involves development of processes to systematically extract, cleanse and classify data on electronic (e)-alerts transmitted by the algorithm of the aforementioned system. This author's work results in a data set which is suitable for analysis and enables reliable identification of all AKI occurring in the Welsh population, including that which is hospital and community acquired. Following this is project two and presentation of a series of peer-reviewed studies by the author which, by utilising the described novel data set, include some of the first comprehensive, population-based descriptions of AKI and its associated factors known to date. Project three follows with further practical examples of work by the author to demonstrate the potential of the same data set. It begins with studies by the author which, in helping end-users better understand the significance of AKI e-alerts, could allay speculation healthcare providers and professionals may have regarding their clinical utility. It closes by presenting a prototype of a tool which, via application of statistical process control techniques and indicators developed by the author, provides a means to robustly measure, and identify variation in, quality of healthcare provision related to AKI in Wales, a mechanism which did not exist prior.

The original contribution to knowledge is the methodological development of a new national data source for AKI, and the demonstration and conclusion that these large validated data provide unique opportunity to reliably inform the epidemiology of, and quality improvement in healthcare provision for, AKI. Work on and of this scale and scope is yet to be achieved elsewhere. This thesis therefore significantly adds to the literature to which it relates. To validate its contribution, and support its overall conclusion, the peer-reviewed status of the author's 14 published works appended and presented throughout are offered. Finally, while the work here concerns SCr and AKI, it is also presented as a wider proof of concept which in theory could be replicated for other routine laboratory-based healthcare data, to improve the epidemiological understanding and management of other health conditions.

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**List of abbreviations**

| | |
|---|---|
| **ADQI** | Acute Disease Quality Initiative |
| **AHW** | A Healthier Wales |
| **AKI** | acute kidney injury |
| **ARF** | acute renal failure |
| **ATN** | acute tubular necrosis |
| **CA** | community acquired |
| **CDSS** | clinical decision support system |
| **CKD** | chronic kidney disease |
| **CQI** | continuous quality improvement |
| **CSV** | comma-separated values |
| **CT** | Cwm Taf |
| **eGFR** | estimated glomerular filtration rate |
| **GFR** | glomerular filtration rate |
| **HA** | hospital acquired |
| **HAQ** | Healthcare and Access Quality Index |
| **HB** | Health Board |
| **HQUIP** | Healthcare Quality Improvement Partnership |
| **IOM** | Institute of Medicine |
| **KDIGO** | Kidney Disease Improving Global Outcomes |
| **NAFLD** | Non-alcoholic fatty liver disease |
| **NCEPOD** | National Confidential Enquiry into Patient Outcome and Death |
| **NHS** | National Health Service |
| **NHSW** | National Health Service in Wales |
| **NICE** | National Institute for Health and Care Excellence |
| **OECD** | Organisation for Economic Co-operation and Development |
| **ONS** | Office for National Statistics |
| **Org** | Organisation |
| **PC** | primary care |
| **PSN** | patient safety notice |
| **QA** | quality assurance |
| **QC** | quality control |
| **QI** | quality improvement |
| **QOF** | Quality Outcomes Framework |
| **RRT** | renal replacement therapy |
| **RV** | reference value |
| **RVR** | reference value ratio |
| **SAKI** | suspected acute kidney injury |
| **SCr** | serum creatinine |
| **SPC** | statistical process control |
| **UHB** | University Health Board |
| **VBHC** | Value Based Healthcare |
| **WDS** | Welsh Demographic Service |
| **WG** | Welsh Government |
| **WHO** | World Health Organisation |
| **WIMD** | Welsh Index of Multiple Deprivation |
| **WLIMS** | Welsh Laboratory Information Management System |

**Copyright declaration**

This is to certify that the work described in this thesis and portfolio is my own. No part of this thesis or portfolio has been presented or is currently submitted in candidature for any degree at any other university.

Signed: *J. Holmes*

Date: 31-*03-2022*

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# Chapter 1: Critical Overview

## 1.1 Introduction and layout of thesis

Acute kidney injury (AKI) is a syndrome characterised by a rapid reduction in kidney function. It is recognised as a global health issue due to its increasing incidence and associated poor outcomes. Improving the prevention and management of AKI is therefore widely accepted as an important goal for the healthcare sector. While improvement science states that without measurement, improvement is not possible, at the outset of this research, the epidemiology of AKI was also not fully understood. This thesis centres on the proposed utilisation of routine SCr data for informing the epidemiology of AKI, and informing improvement in care for patients who develop and/or are at risk of, AKI. The overarching theme of this research can therefore be described as the application of routine population healthcare data for epidemiology and quality improvement (QI) in care.

This opening critical overview chapter outlines the three separate but intrinsically linked research projects that comprise this 'PhD by portfolio' style thesis (Figure 1.1). In introducing the key concepts underpinning these projects, and presenting the broader theory in which the thesis sits, it provides the context for the author's work that is documented. This chapter also discusses the conclusions and limitations of the research as a whole and concludes by demonstrating its original contribution to knowledge, summarising its potential implications for policy, practice and theory, and offering a number of recommendations for future work.

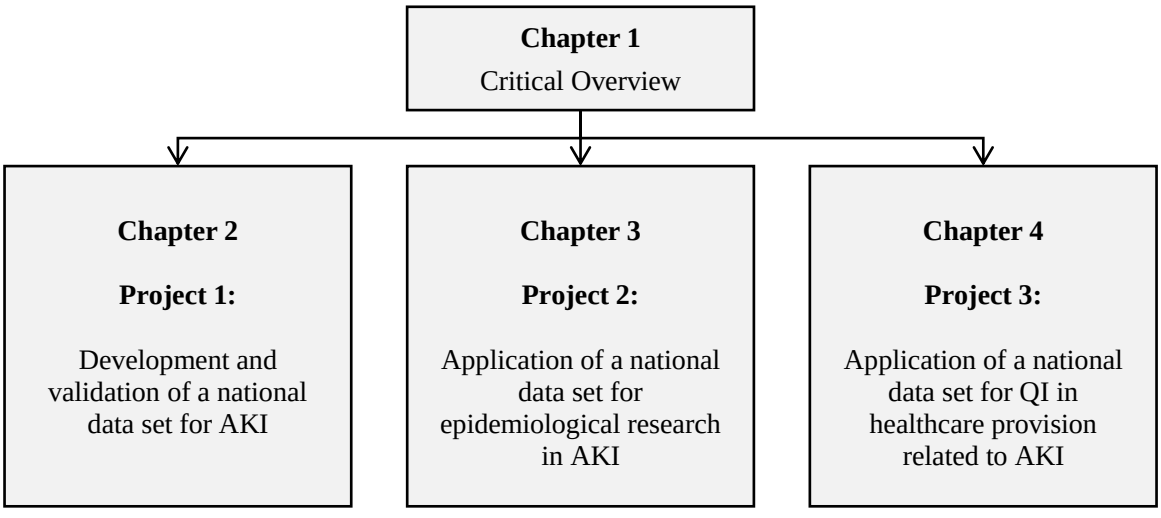



**Figure 1.1:** Structure of 'portfolio style' thesis

## 1.2 Origins of thesis

A recent National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2009) identified significant systemic deficiencies in healthcare provision for AKI across the UK. In its review of care of patients who died in hospital in England and Wales with a primary diagnosis of AKI, it found a high proportion of care to be suboptimal, with only 50% of patients with AKI considered to have received a 'good' standard of care. The so-called 'Adding insult to injury' report also found 30% of the AKI cases it reviewed were preventable. Despite its reliance on hospital coding data which is often prone to error, and a patient population in which all outcomes were death, the enquiry described was evidence of AKI, in some cases, causing avoidable harm and death. Smaller local Welsh studies conducted soon after (Talabani *et al*., 2014; Wonnacott *et al*., 2014) also identified similar sub-standard care for AKI.

Following NCEPOD, the National Institute for Care and Excellence (NICE, 2013) issued, for the first time, guidelines on the prevention, detection and management of AKI. This coincided with the development of new internationally agreed biochemical diagnostic criteria for AKI, by the 'Kidney Disease: Improving Global Outcomes' working group (KDIGO, 2012). Also following this was the launch by the International Society of Nephrology of their '0by25' initiative, setting out a worldwide ambition to prevent all avoidable death from AKI by 2025 (Mehta *et al*., 2015).

The events described brought political attention to AKI in the UK which in turn prompted widespread calls for the development of new strategies to improve its prevention and management. In Wales, this involved the issue by Welsh Government (WG) of a patient safety notice for AKI (Appendix 1.1), and the establishment of a national AKI Steering Group, a taskforce set up to develop a standardised approach to AKI across the National Health Service in Wales (NHSW). This approach included the development and implementation of a national automated laboratory-based clinical decision support system (CDSS) for AKI, based on the assumption that this would aid early recognition and intervention of AKI, and thereby improve patient outcomes (Feehally *et al*., 2013).

The improvement science literature states that without measurement, improvement is not possible (Deming, 1986; Drucker, 1997). Palmer (1998) says that in QI, improvement is the goal of measurement. If the quality of healthcare provision related to AKI in Wales was to improve, it therefore needed to be measurable. In addition to its clinical application, the forementioned CDSS or electronic (e)-alerting system for AKI, which had been implemented by all laboratories in NHSW, also had the potential to be applied as a centralised system of data collection, to systematically collect national data on AKI. This large source of data may have offered

opportunity to firstly, better understand the epidemiology of AKI, and secondly, inform strategies aimed at improving the prevention and/or management of AKI.

## 1.3 Research question and aims

This healthcare informatics thesis explores the research question:

> *Does application of routine population healthcare data offer the opportunity to inform and improve care?*

Specifically it asks whether a national AKI alerting system, which utilises routine SCr data, can be applied to:

(i) inform the epidemiology of AKI, and
(ii) inform improvement in care for patients who develop and/or are at risk of AKI.

To answer these questions, the overall aims of the thesis are as follows:

1. To develop a validated national data set for AKI.
2. To explore and demonstrate the potential of these data for epidemiological research in AKI.
3. To explore and demonstrate the potential of these data for QI in healthcare provision related to AKI.

## 1.4 Acute Kidney Injury

Kidneys play a key role in maintaining homeostasis in the human body and are responsible for the filtration and excretion of metabolic waste products from the bloodstream. An acute injury to the kidney can broadly be defined by a rapid decline in the glomerular filtration rate (GFR) - the flow rate of filtered fluid through the kidney – resulting in the retention by the body of metabolic waste products (Thadhani *et al*., 1996). Creatinine is one example of these products. The breakdown product of Creatine, it is produced as a result of muscle protein metabolism, and is released by the body at a constant rate. Comparative measurements of this compound in the blood, otherwise known as Serum Creatinine (SCr), can therefore be used to reliably indicate changes in GFR, where increasing levels of SCr reflect a decreasing GFR. While other biological markers such as Inulin and Cystatin-C may be more sensitive to changes in kidney function, using these alternative agents to estimate GFR requires complex and expensive chemical assays which are

impractical for routine use (Basile *et al*., 2012; Edelstein, 2008; Makris and Spanou, 2016). SCr therefore remains the biomarker most routinely used in clinical practice for measuring renal function (KDIGO, 2012), with Waikar *et al*. (2013) describing it as the 'imperfect gold standard' for such. SCr is therefore also the diagnostic test used by the AKI alerting system described in this thesis to detect AKI.

Historically, and to acknowledge the continuum of injury which can occur before kidney function fails, AKI replaces acute renal failure (ARF). Whilst first used by American physician William MacNider in 1918, AKI did not become the preferred term until the early 21st century, until which ARF and acute tubular necrosis (ATN) were used interchangeably. During this time, consensus classifications of ARF and/or ATN also did not exist and in their scientific survey of the literature, Kellum *et al*. (2002) found over 35 different definitions for AKI and its relative aliases.

### 1.4.1 Epidemiology of AKI

Delay in a universal definition meant that at the outset of this thesis, the epidemiology of AKI was not fully understood. While population incidence of AKI was reportedly rising (Rewa and Bagshaw, 2014; Lameire *et al*., 2013; Xue *et al*., 2006; Hsu *et al*., 2007), the incidence reported in the literature varied depending on the definition used and clinical and geographical setting studied. The majority of large scale studies had mostly also relied upon hospital coding data or retrospective review of patient records for identification of AKI, methods which are prone to inaccuracy and can lead to missed cases (Bucaloui *et al*., 2012; Hsu *et al*., 2007; Liangos *et al*., 2006). Although providing some key information on the epidemiology of AKI, these studies likely therefore underestimate the actual incidence of AKI. While some studies had sought to overcome this by using biochemical criteria to identify their AKI patient cohorts, these were either single-centre based (Porter *et al*., 2014, Wallace *et al*., 2014), or used e-alert systems not based on the new and forementioned internationally agreed definition of AKI formulated by KDIGO (Thomas *et al*., 2011; Amin *et al*., 2012). Most epidemiological AKI research prior to this thesis had mostly also concentrated on the inpatient and critical care setting (Chertow *et al*., 2005; Rewa and Bagshaw, 2014; NCEPOD, 2009) and less was known about AKI in the community setting. While it had been reported that 60% of hospitalised AKI patients actually acquire their injury in the community, and nearly 50% of community acquired (CA) AKI is not admitted to hospital (Selby *et al*., 2012; Wonnacott *et al*., 2014), studies characterising CA-AKI had mainly relied on small samples and because of geographic differences in disease patterns, may not have been directly applicable to all populations (Cui *et al*., 2005; Daher *et al*., 2012; Obialo *et al*., 2000; Talabani *et al*., 2014). By providing a comprehensive epidemiological description of AKI in the entire Welsh population, including that acquired in the hospital and community setting, studies conducted by the author presented as part of this thesis address some of these deficiencies in the literature.

While at the outset of this thesis the incidence of AKI may have been rising, and reportedly driven mostly by an increasingly ageing and comorbid population (Horton and Berman, 2015; Xue *et al*., 2006; Hsu *et al*., 2007), it was also known that patients who develop AKI experience poor outcomes, even in its milder forms. These include but are not limited to an increased likelihood of death, with in-hospital mortality following AKI found to be as high as 35% for patients requiring treatment by renal replacement therapy (RRT), an increased risk of subsequent development and/or progression of chronic kidney disease (CKD), increased morbidity, and lower quality of life (Rewa and Bagshaw, 2014; Ali *et al*., 2007; Bagshaw *et al*., 2005; Waikar *et al*., 2008; Wald *et al*., 2012; James *et al*., 2020).

AKI is simultaneously associated with poor consequences for healthcare providers. These mainly include the economic implications resulting from those patients who survive but fail to recover renal function following their AKI and who therefore consume substantially more healthcare resource as a result of their CKD, long-term requirement for RRT, repeated and prolonged hospitalisations, and increased need for critical care (Rewa and Bagshaw, 2014). For the healthcare economy, AKI is therefore among one of the most expensive health conditions, with NICE (2019) previously estimating that management of non-community related AKI costs the NHS in the UK between £434 and £620 million per year, more than the cost of some common cancers combined.

### 1.4.2 Prevention of AKI

If AKI has poor outcomes for patients and providers, it is important that where possible, it is prevented. While NCEPOD (2009) report that up to 30% of in-hospital AKI is avoidable, NICE (2013) have previously estimated that strategies aimed at reducing AKI in the UK could result in up to 100,000 fewer cases and 42,000 less deaths per year.

The notion of prevention over intervention as a form of treatment is well known and Kam Tao Li *et al*. (2013) say most causes of AKI could be prevented at the individual, hospital, community or regional level. While it can occur in anyone, a number of factors can increase one's risk of developing AKI. They include but are not limited to increased age, history of AKI, and chronic conditions such as CKD, heart and liver failure, and diabetes (Makris and Spanou, 2016). Kashani *et al*. (2019) extend this risk profile further and categorise risks as those which are inherent and non-modifiable, those which are exposure-based, those which are caused by care processes, and those which are associated with socioeconomic and environmental factors.

In their extensive guidance for preventing both nosocomial AKI and AKI in the community, NICE (2013) recommend identifying at risk patients so that their renal function can be monitored, and

hydration and avoidance of nephrotoxic drugs can be ensured. The Acute Disease Quality Initiative (ADQI) agree. Whilst they suggest mitigating the incidence of AKI involves identifying and monitoring high risk patients, in their series of recommendations regarding the role of healthcare systems in preventing AKI, they also advise monitoring variation in population-based AKI incidence, and improving patient education and awareness of AKI (Kashani *et al*., 2019). Kellum *et al*. (2012) go further and to highlight the significance of the condition among the public, suggest describing an AKI as a 'kidney attack'. Although awareness raising may not be the scope of this work, by providing a means to monitor the incidence of AKI in the Welsh population, and exploring factors associated with variation in its incidence, the work here is nonetheless pertinent to the other recommendations described.

### 1.4.3 Management of AKI

While prevention is important, not all AKI is preventable. However, through early identification and correct treatment, most AKI is reversible (NICE, 2013). Because it occurs rapidly and often without symptoms in the early stages, diagnosis and treatment of AKI can however be complex and is further complicated by its diverse aetiology (Basile *et al*., 2012). Although a disease of the kidney, variation in its presentation across different care settings also means the majority of AKI is not seen nor managed by a nephrologist. It is therefore key all care professionals, not just those within the renal specialties, understand the significance of rises in SCr and are able to detect and manage AKI (Thornburg and Gray-Vickrey, 2016; Makris and Spanou, 2016). While many factors may explain the inconsistent management of AKI from which this thesis originates (NCEPOD, 2009), and while unlikely a problem exclusive to the Welsh healthcare system (Forde *et al.*, 2012), the forementioned CDSS was one intervention implemented in NHSW to address this suspected and so-called 'AKI ownership' issue. Another was the production of a national care protocol for patients presenting with AKI (Appendix 1.2), based on the premise that care protocols align clinical practice with evidence-based guidelines (Campbell *et al*., 1998). Whether the interventions described actually improved clinical management of AKI in Wales as intended is not necessarily the focus of this thesis however. Rather, the work here is the precursor to, and provides the means for, potential QI work like this.

## 1.5 The Welsh AKI alerting system

If this thesis applies the Welsh AKI alerting system as a centralised system for data collection, a baseline technical understanding of this system is necessary to interpret the author's work that is presented.

### 1.5.1 AKI algorithm

A CDSS, of which the Welsh AKI alerting system is an example of, involves two automatic processes; a diagnosis, involving an algorithm performing a calculation, or series of calculations, and a notification, involving the same algorithm communicating the outputs of its analysis to a relevant clinician. Figure 1.2 illustrates the process by which alerts are triggered by the Welsh AKI alerting system. Its algorithm (Figure 1.3) automatically, in real-time and at point of testing, compares for an individual patient, a current SCr result value with previous SCr results. Based on the forementioned KDIGO definition of AKI, the alert algorithm is designed to detect possible incident cases of AKI by applying three different rules. These rules are based on absolute or relative increases in SCr from a baseline reference SCr value that has been drawn either from the previous 48 hours (Rule 1), 7 days (Rule 2), or 8-365 days (Rule 3) (Table 1.1). Specifically, the algorithm first generates two different reference values: the lowest SCr from the previous 7 days (RV1), and the median SCr from the previous 8-365 days (RV2). By dividing the current SCr value by each RV, it then calculates two reference value ratios (RVR) and selects the highest. If the higher RVR is greater than or equal to 1.5, and the current SCr can therefore be described as being at least 50% greater than either RV1 or RV2, an alert is triggered. Depending on the size of the observed increase in SCr, alerts are then classified for severity, as either stage 1, 2 or 3, and where a higher stage indicates a higher severity (Table 1.2). Where the highest RVR is less than 1.5 but an increase of more than 26 μmol/L in the previous 48 hours can be observed, the algorithm will trigger a stage 1 alert (Table 1.3). If neither an increase of more than 26 μmol/L in the previous 48 hours or a RVR greater than or equal to 1.5 can be observed, no alert is triggered.

### 1.5.2 AKI alerts

Combining the three algorithm rules with the three AKI stages results in nine distinct possible algorithm outputs, or alerts, with a different code generated for each (Tables 1.3 and 1.4). In addition to these nine alerts, the algorithm also triggers alerts for suspected AKI, with code 'SAKI'. These however do not represent actual AKI based on the KDIGO definition, and are triggered to warn clinicians of possible developing cases of AKI.

### 1.5.3 Scope of system

All 19 laboratories in NHSW use the centralised Welsh Laboratory Information Management System (WLIMS), an 'InterSystems TrakCare Lab' database for the administration of test results, including SCr. These laboratories undertake biochemistry investigations on behalf of all NHSW healthcare professionals, from all sectors of the healthcare system, including both primary and secondary care. Except for the small number of Welsh residents who may access care over the border, the WLIMS therefore records and stores data on all laboratory tests conducted for the 3.3 million people of Wales (ONS, 2020), with over 1.8 billion rows of data at time of writing. By being based in the WLIMS, and since its activation in April 2015 (Table 1.4), it is therefore possible to apply the described AKI alert algorithm to collect data on all AKI events occurring in the entire Welsh population, including that diagnosed in the hospital and community setting. A system with such national and cross-sector scope is yet to be proven elsewhere and is why much of the work described in this thesis is unique.

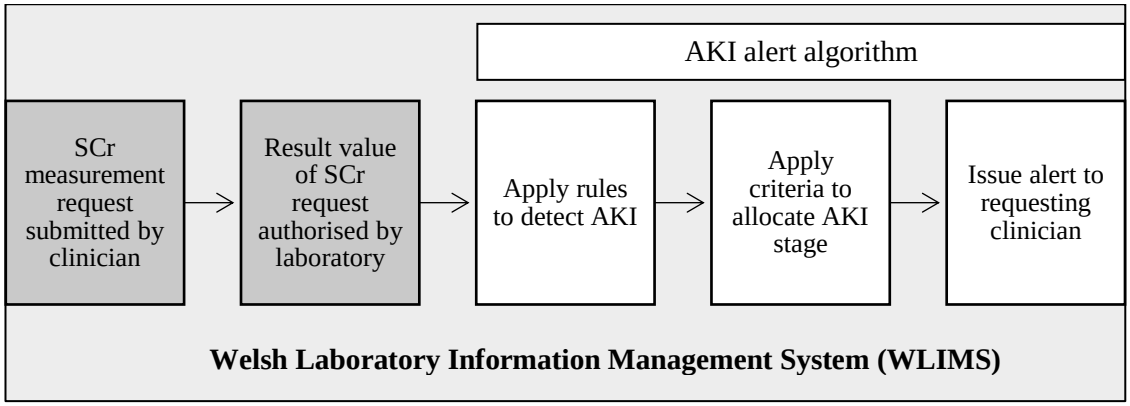



**Figure 1.2**: Process by which electronic AKI alerts are triggered in the WLIMS

**Table 1.1:** Rules applied by the Welsh AKI alerting system to detect AKI

| Rule | Reference value (RV) | AKI alert trigger criteria |
|---|---|---|
| Rule 1 | Lowest SCr from previous 48 hours | No other rule triggered and more than a 26 µmol/L increase in SCr from RV |
| Rule 2 | Lowest SCr from previous 7 days | At least a 50% increase in SCr from RV |
| Rule 3 | Median SCr from previous 8-365 days | At least a 50% increase in SCr from RV |

**Table 1.2:** AKI staging criteria applied by the Welsh AKI alerting system

| AKI Stage | SCr criteria |
|---|---|
| Stage 1 | 50-99% increase OR an increase of more than 26 µmol/l (0.3 mg/dL) |
| Stage 2 | 100 to 199% increase |
| Stage 3 | At least a 200% increase OR an increase to at least 354 µmol/l (4.0 mg/dL) |

**Table 1.3:** AKI alert codes triggered by the Welsh AKI alerting system for adult patients

| Alert code | Trigger criteria | Rule | Stage |
|---|---|---|---|
| DELTA1 | D >26 µmol/L AND no other rule triggered | 1 | 1 |
| ABS1 | C1/RV1>C1/RV2 AND C1/RV1≥1.5 AND C1>354 µmol/L | 2 | 3 |
| ABS2 | C1/RV2>C1/RV1 AND C1/RV2≥1.5 AND C1>354 µmol/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 |
| SAKI | C1-RV1>26.5 µmol/L AND no other rule triggered | n/a | n/a |

*C1, Current SCr value authorised in the WLIMS; RV, Reference SCr value with which C1 is compared; RV1, lowest SCr result from previous 7 days; RV2, median of SCr results from previous 8-365 days; D, Difference between C1 and lowest SCr result from previous 48 hours.*

**Table 1.4:** AKI alert codes triggered by the Welsh AKI alerting system for paediatric patients

| Alert code | Trigger criteria | Rule | Stage |
|---|---|---|---|
| DELTA1 | D >26 µmol/L AND no other rule triggered | 1 | 1 |
| ABS1 | C1/RV1>C1/RV2 AND C1/RV1≥1.5 AND C1> 3 times the upper limit of age and sex related population reference range for SCr | 2 | 3 |
| ABS2 | C1/RV2>C1/RV1 AND C1/RV2≥1.5 AND C1> 3 times the upper limit of age and sex related population reference range for SCr | 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 |
| SAKI | C1-RV1>26.5 µmol/L AND no other rule triggered | n/a | n/a |

*C1, Current SCr value authorised in the WLIMS; RV, Reference SCr value with which C1 is compared; RV1, lowest SCr result from previous 7 days; RV2, median of SCr results from previous 8-365 days; D, Difference between C1 and lowest SCr result from previous 48 hours.*

**Table 1.5:** Implementation of the Welsh AKI alerting system across NHS Wales

| NHS Wales organisation | Date active | Number of laboratories | Population served* |
|---|---|---|---|
| Cwm Taf UHB | November 2013 | 2 | 296,735 (9.6%) |
| Hywel Dda UHB | December 2013 | 4 | 383,229 (12.4%) |
| Aneurin Bevan UHB | March 2014 | 3 | 581,789 (18.8%) |
| Betsi Cadwaladr UHB | September 2014 | 3 | 694,473 (22.4%) |
| Cardiff and Vale UHB | November 2014 | 2 | 484,752 (15.6%) |
| Velindre NHS Trust** | November 2014 | 1 | n/a |
| Abertawe Bro Morgannwg UHB | March 2015 | 4 | 525,466 (17.0%) |
| Powys Teaching HB*** | March 2015 | 0 | 132,642 (4.3%) |

**Population based on ONS mid-year 2016 estimates. **Velindre NHS Trust manages and provides care for the population accessing cancer care in Wales, rather than a regional population of Wales. ***Powys Teaching Health Board is served by laboratories in neighbouring Health Boards. UHB, University Health board.*

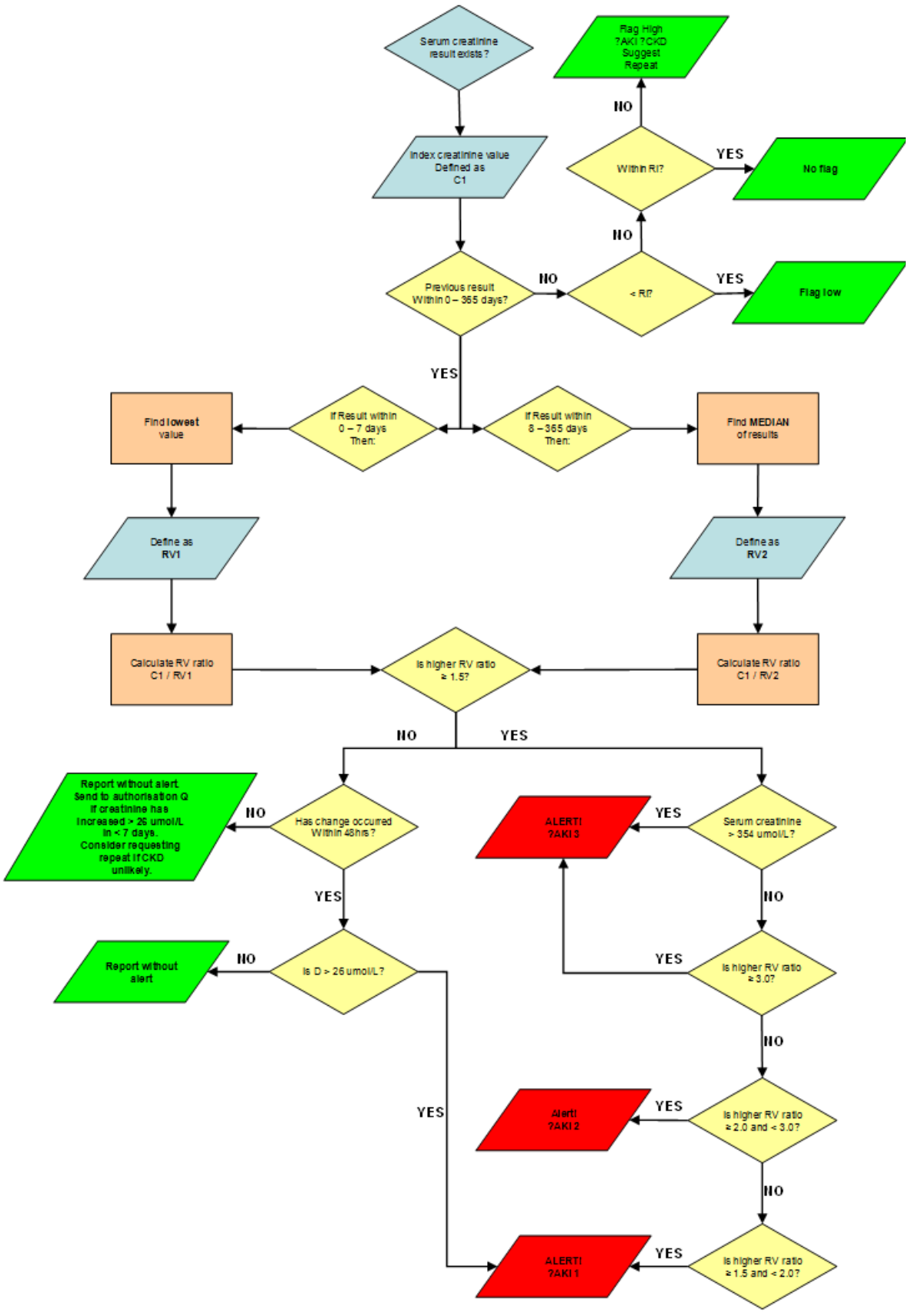



**Figure 1.3:** National AKI alert algorithm, based on changes in SCr over time.
*C1, Current SCr value authorised in the WLIMS; RV, Reference SCr value with which C1 is compared; D, Difference between C1 and lowest SCr result from previous 48 hours; RI, Population reference interval.*

## 1.6 Quality in healthcare

If this thesis is to utilise the described national AKI alerting system for data collection, and demonstrate the potential of these data to inform and ultimately improve quality of care for patients who develop and/or are at risk of AKI, a theoretical understanding of quality and QI is required. Management theorist Drucker (1997) famously claimed "*if you can't measure it, you can't improve it*". For quality to improve it therefore must be measurable and if it is to be measured, it first must also be defined.

### 1.6.1 Quality

Derived from the Latin 'qualis', meaning 'what kind of', quality is defined in the Oxford English Dictionary (1997) as "*the standard of something when it is compared to other things like it*". The earliest transcendent definition of quality in the context of healthcare came in 1960 from American physician and researcher, Donabedian (1988), when he described it as:

> "*care which is expected to maximize an inclusive measure of patient welfare, after one has taken account of the balance of expected gains and losses that attend the process of care in all its parts*".

Indicating the movement in medicine towards more evidence-based approaches, the Institute of Medicine (1990) later defined quality of care as:

> "*the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge*".

The latest universally recognised definition is that by the WHO (2018), who define it simply as services which are safe, effective, and person-centred. Despite the vast literature and debate of these three dimensions (Busse *et al*., 2019), the definition of quality in healthcare remains vague. Given care is intangible, it is often difficult to operationalise. This can make its measurement in practice challenging and despite work like that of Mainz (2003b), providing detailed primers for developing indicators of healthcare quality, Campbell *et al*. (2002) suggest a perfect measure of quality of care, for any condition, is unlikely achievable. The Donabedian framework is nonetheless the most widely accepted approach for evaluating quality of care (Busse *et al*., 2019; Donabedian, 1988) and hypothesises that good structure increases the likelihood of good process, which in turn increases the likelihood of good outcome.

Research to date on the development and application of quality indicators in the field of AKI is limited. While some have combined evidence, opinion and guidelines to recommend indicators

for measuring the quality of AKI care (Kashani *et al*., 2019; Macedo *et al*., 2020; Liu *et al*., 2020), less have demonstrated their application (Mehboob *et al*., 2018; Shen *et al*., 2018; Tsang *et al*., 2021). Work aimed at developing indicators for effectively measuring improvement in the prevention and management of AKI is therefore regarded both a clinical and research priority (James and Pannu, 2015; Kashani *et al*., 2019; Macedo *et al*., 2020; Liu *et al*., 2020).

### 1.6.2 Quality improvement

QI can generally be described as a systematic approach that uses specific techniques to improve quality (WHO, 2018). Ovretveit (2009) calls QI in healthcare better patient outcomes achieved by changing provider behaviour using systematic change strategies. Shojania *et al*. (2004) meanwhile say it involves strategies for closing 'quality gaps', that is, differences between accepted best care practices and actual care delivered. Continuous quality improvement (CQI) is a wider concept which states successful QI relies not only on timely and reliable information, as this thesis seeks for AKI in Wales, but on wider system factors also. Anderson *et al*. (1994) suggest while robust measurement is important, sustained improvement requires a systems based approach involving behaviour change and commitment from the entire organisation. While these other elements are worth acknowledging, they are however not within the scope of this research, which instead is concentrated on the role of measurement in the QI process.

The QI measurement process, and therefore this thesis, utilises statistical process control (SPC) methodology. SPC can be used to scientifically identify statistical variation in data over time. Discussed at greater length in project three of the thesis, SPC historically originates in quality control (QC) and quality assurance (QA), systems to verify, maintain, and prevent defects in, a desired level of quality (Feigenbaum, 1991). While distinction between the three concepts can be useful, their differences are not always clear and in reality, QA is often an element of and/or tool for QI (Busse *et al*., 2019; Juran 1986). The author therefore theorises that although initially supposed for QI, the work here also leans heavily on the principles of QA and broader concept of quality management.

### 1.6.3 Quality and healthcare policy

The political importance of QI in healthcare evolved globally following two landmark studies by the Institute of Medicine (IOM): 'To Err Is Human' (IOM, 1999), which highlighted up to 98,000 deaths occur annually due to medical error, and 'Crossing the Quality Chasm' (IOM, 2001) which built on the former and called for fundamental change in healthcare systems. With 'quality of care' one of the most quoted principles in health policy worldwide (OECD, 2017; WHO, 2018), policymakers today universally acknowledge its importance.

The WHO (2018, p.10) suggest all countries should have a national health quality policy, "*an explicit statement of intention with an agreed course of action*". In Wales, this is WG's current 'A Healthier Wales' (AHW) strategy, which sets a vision for a whole system approach to health and social care and in which 'quality' is mentioned 51 times (Welsh Government, 2018). Beneath AHW lies the long term strategy of Public Health Wales (2018, p.9), in which one of its seven priorities includes "*development of a sustainable health and care system focused on prevention and early intervention*", and to which this thesis also aligns well.

### 1.6.4 Value and quality

QI is commonly associated with increased efficiency and therefore value. Ovretveit (2009) writes that improving quality contributes to cost-efficiency and while policymakers recognise the importance of QI for raising standards of care, it is also widely accepted that public resources are finite (Busse *et al*., 2019). Hence, although publically funded healthcare systems like NHSW are not profit driven, effective and efficient allocation of resource is also important and emerging value-based healthcare (VBHC) agendas can now be observed worldwide.

Simply described, VBHC aims to minimise unwarranted variation in healthcare systems to maximise their value for the populations they serve (Porter, 2010). The VBHC approach first seeks to identify whether current service delivery models generate the best outcomes and then focusses on reallocation of resource into high value interventions to achieve better outcomes. Former Deputy Chief Medical Officer for Wales states:

> "*We must look at how we currently deliver services and whether everything we do contributes to the best outcomes for people. Surprisingly, not everything does. We therefore need to do less of the things that don't help, and reinvest that money into doing more of the things that do. This is what we mean by 'Value Based Health Care'."* (Value in Health, 2020, p.2).

In Wales, VBHC is enforced by the forementioned AHW strategy, in which 'Higher value' represents one of ten principles and seeks to achieve "*better outcomes at reduced cost, delivery of care by the right person at the right time, less variation and no harm*" (Welsh Government, 2018, p.17). The NHSW VBHC paradigm, of which health informatics is a key component (Figure 1.4), also suggests a data-driven approach is critical for driving QI, a view also echoed by the overarching theme of this research.

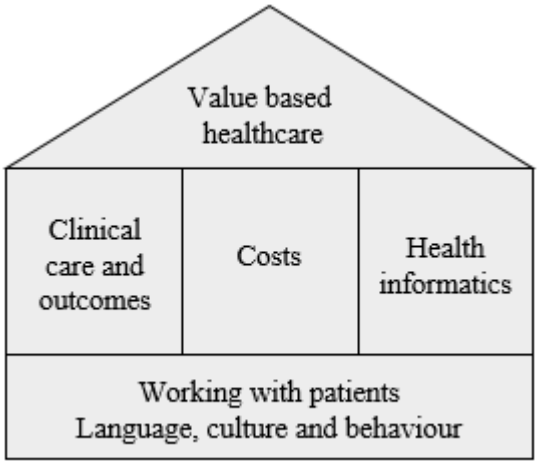



**Figure 1.4:** Value-based healthcare paradigm. *Adapted from: Value in Health (2020, p.7).*

### 1.6.5 Quality assurance in NHS Wales

While policy is one, other structures at the organisational, national or international level for monitoring, quantifying, and ultimately assuring quality of care can include governance models and/or institutions (Busse *et al*., 2019). The QA infrastructure in Wales is underpinned by the NHSW health and care standards performance framework, against which WG hold NHSW organisations to account. It monitors data on almost 100 measures and includes an escalation system if pre-set standards are not met (Willson and Davies, 2020). In line with NHS performance reporting elsewhere in the UK, some of these quality indicators are made publically available, including information on waiting times, accident and emergency admissions, bed occupancy rates, ambulance response times, and more recently, Coronavirus (Welsh Government, 2021). WG also meanwhile have sight of other internally published NHSW healthcare data such as that relating to serious incidents, patient safety alert compliance, health care acquired infection, pressure ulcer incidence, mortality and avoidable deaths (OECD, 2017).

While a 2016 review by the OECD (2017) praised what they described as an already rich healthcare QA architecture in Wales, it also identified potential opportunities for improvement and made a series of recommendations. In highlighting the importance of robust performance measurement and NHSW becoming an evidence- and data-driven system, this included suggesting available data be brought together in a more user-friendly format, and in as close to real-time as possible. While the described review may pre-date WG's forementioned AHW strategy and the advent of some disease management tools since published by Digital Health and Care Wales (2021), including for lung cancer and heart failure, the author proposes the work here as pertinent to these calls for increased and better utilisation of data for monitoring and improving care across the principality.

### 1.6.6 Indices of healthcare quality

Stakeholders recognise that without reliable information on quality of care, it is difficult to assure it. Measurement and comparison of performance of providers is therefore essential to deliver quality care (Busse *et al*., 2019). These 'benchmarking' systems are sometimes described as healthcare quality indices, or indexes, and one example is that by the OECD, which has been collecting and reporting internationally comparable information on healthcare quality since 2001 (Busse *et al*., 2019). Another is the 'Healthcare and Access Quality index' (HAQ), which ranks countries by amenable mortality, defined as deaths that should not occur in the presence of effective care (Fullman *et al*., 2017). While indices like these offer international comparison of health outcomes, less common are reliable benchmarks at lower levels such as the national and organisational level, or as Carini *et al*. (2020) theoretically describe it, measurement of performance of nodes within networks. Benchmarking the performance of care providers in and between the UK has historically been mixed. This is criticised by some who say although the funding structures of the four UK nations may differ, their health systems and populations are fundamentally similar, and therefore provide significant opportunity for comparative performance data. The OECD (2017) have previously called for:

> "*a set of key health data and quality indicators for all UK health systems, collected using agreed common definitions, to facilitate quality and performance benchmarking."*

Despite efforts such as the Quality Outcomes Framework (QOF, 2015) and Healthcare Quality Improvement Partnership (HQUIP, 2018), political and technical challenges have so far made this difficult. The author speculates that some of the work in this thesis could contribute to discussions regarding further future UK wide efforts like these.

## 1.7 Summary of projects

Three research projects are documented in this portfolio style thesis and independently and collectively answer the overall research question.

### 1.7.1 Research governance

Full ethical approval for the work documented was obtained by NHSW Service Evaluation Project Registration on 1st June 2014 (Ref: CT/428/14). As the approving organisation, Cardiff and Vale University Health Board issued the approval document, as signed and approved by the Caldicott Guardians of all NHSW organisations. This document permitted the national AKI steering group and author of this thesis routine access to data from the WLIMS on all patients for which the

described national AKI alert algorithm had triggered an alert.

### 1.7.2 Project 1: Development and validation of a national data set for AKI

In the quality literature, Deming (1986) describes quality as 'fitness for use'. In the context of data, this translates to data that are fit for use by its consumer and which can meet their specific goals. If data on AKI alerts triggered by the Welsh AKI alerting system were to be used for epidemiological research in AKI and/or inform improvement in healthcare provision related to AKI, it was important that first, processes for generating these large data sets were developed, and second, these data were also 'fit for use'. In addressing the first aim of the thesis, this first project describes the work undertaken by the author to develop a validated and 'fit for use' national data set for AKI. By applying the Welsh AKI alerting system as a centralised system of data collection, it describes the development of processes by the author to systematically and reliably extract national data on AKI alerts from the WLIMS. It also describes the development of processes by the author to cleanse these data, so that they could be considered suitable for analysis. To ensure a reported clinical setting which best represents the actual clinical setting of the AKI, it also documents work undertaken by the author to develop a method which could be used to, automatically, using the data, classify the clinical setting of alerts, as either hospital acquired (HA) or community acquired (CA) AKI. Finally, because not all AKI alerts can be assumed to represent a distinct clinical episode of AKI, it also documents work undertaken by the author to develop a method to automatically, using the data, distinguish between AKI alerts and incident episodes of AKI, to thus ensure a calculated incidence that best represents the actual incidence of AKI.

To position this initial project into the context of the overall thesis, it provides the data set and methods with which to classify and analyse forementioned data set, so that it can be used to reliably identify all AKI events occurring in the entire Welsh population, and to robustly calculate an incidence of HA- and CA-AKI which best reflects the actual clinical incidence of AKI in the country of Wales. A data set with this scale and scope is yet to be proven elsewhere. The work of this first project therefore underpins the remaining work documented in the thesis, and also provides the necessary confidence in its presented findings and conclusions.

### 1.7.3 Project 2: Application of a national data set for epidemiological research in AKI

As previously discussed, and at the outset of this research, the epidemiology of AKI was not fully understood. While numerous studies had described AKI that is developed during hospitalisation, less had focused on AKI that is developed in the community. The improvement science literature

also states that if something is to improve, it first must be measured (Deming, 1986; Drucker, 1997). If the provision of care for patients in Wales who develop and/or are at risk of AKI was to be improved, it was therefore important that before this, the nature and burden of the condition was first fully understood. In addressing the second aim of the thesis, this second project includes a series of peer-reviewed studies by the author which, by utilising the data set developed in project one, collectively provide a comprehensive epidemiological description of AKI. The 11 published works presented (Appendix 3.1-3.11) follow two themes; they either define and describe the incidence and outcome of AKI in a selected patient population and/or healthcare setting, and/or they explore factors associated with variation in the incidence and/or outcome of AKI. This included analysis of AKI in the:

- adult,
- paediatric, and
- renal transplant populations of Wales, and in the
- hospital,
- community,
- primary care, and
- intensive care setting.

And the analysis of AKI in association with the following factors:

- age,
- pre-existing CKD,
- socioeconomic status,
- local health board area,
- severity of the AKI,
- clinical specialty associated with the AKI,
- hospitalisation following AKI,
- interaction with healthcare services prior to AKI,
- follow-up care following AKI,
- seasonal variation,
- the ‘weekend effect’, and
- repeated episodes of AKI.

For each publication presented, the abstract followed by an evaluation of the work in the context of the overall thesis is provided.

### 1.7.4 Project 3: Application of a national data set for QI in healthcare provision related to AKI

While project two can primarily be described as documenting the potential of the data set developed in project one for informing the epidemiology of AKI, in addressing the third and final aim of the thesis, this final project documents practical examples of these data's potential for informing QI in healthcare provision related to AKI. Comprised of two parts, it first presents two peer-reviewed studies by the author which by utilising forementioned data set, sought to explore potential opportunities to refine the clinical utility of the AKI alerting system described in this thesis. These studies (Appendix 4.1-4.2) followed concern among some clinicians that such systems could generate large numbers of alerts which could lead to so-called 'alert fatigue', whereby alerts are missed and/or ignored by clinicians regardless of their importance. This was problematic and risked undermining the primary purpose of the system.

While the author's epidemiological studies presented in project two may provide a baseline from which the impact of interventions aimed at improving the quality of healthcare provision related to AKI in Wales could be measured, it was also important for quality to be measurable over time. Without measurement, it is impossible to determine if, and to what extent, interventions improve quality as expected. The second part of this final project describes work undertaken by the author to develop a tool which could be used to robustly measure, monitor and compare the quality of healthcare provision related to AKI in Wales, a mechanism which did not exist prior. This included:

- Using the earlier described Donabedian framework to develop indicators which could be used to measure quality of healthcare provision related to AKI, including: rate of AKI incidence, to measure quality of care for patients at risk of AKI, and rate of 30-day AKI associated mortality, to measure quality of care for patients who develop AKI.
- Exploring the following SPC techniques to analyse, and identify and investigate variation in, quality of healthcare provision related to AKI:
    - control charts,
    - funnel plots, and
    - Pareto charts.
- Building a prototype tool in an appropriate software (Appendix 4.3).

To demonstrate the potential of the described tool for QI, the project concludes with a further and final peer-reviewed study by the author (Appendix 4.4).

## 1.8 Conclusion

Following the work conducted by the author which has involved application of the Welsh AKI alerting system as a centralised system of data collection, this thesis can conclude that a national AKI alerting system, which utilises routine SCr data, provides unique opportunity to:

- inform the epidemiology of AKI, and
- inform improvement in care for patients who develop and/or are at risk of AKI.

Three projects have independently and collectively demonstrated this. While project one first describes the methodological development of a validated 'fit for use' national data set for AKI, projects two and three have explored and demonstrated the potential of these data for epidemiological research in AKI, and QI in healthcare provision related to AKI. In turn, and to answer the overall research question of the thesis, the work documented therefore provides proof of concept that application of routine population healthcare data offers significant opportunity to inform and improve care. As supplementary evidence to support this overall conclusion, the author offers the peer-reviewed status of the 14 published works presented throughout (Appendix 1.3).

## 1.9 Research implications

The author proposes the work presented in this thesis has a number of implications for policy, practice and theory. Primarily, and from a practical perspective, it has provided a novel means to measure, and therefore improve, the quality of care for patients in Wales who develop and/or are at risk of, AKI. The new national source of data it has developed can be used to reliably identify all AKI events occurring in the entire Welsh population, and reliably calculate an incidence of HA- and CA-AKI in this population. A data set with this scale and scope is yet to be proven elsewhere. To compliment this validated data set, the author offers the tool presented in project three, to robustly measure, monitor and compare rates of AKI incidence and AKI associated mortality across all of Wales, a mechanism which also did not exist prior. The tool described could be used by healthcare providers in NHSW to identify opportunities for, and evaluate the impact of, QI in healthcare provision related to AKI. With the potential to identify areas of both high and low relative performance, the author proposes the tool to both reactively and proactively improve care and facilitate the spread of good and/or best practice to areas where performance is suboptimal.

While the focus of this thesis has been QI, the data set it has produced likely has other benefits for policymakers and care providers in Wales. These data could for instance also inform Welsh policymaking concerning AKI, resource allocation for AKI, and help design future AKI service delivery models. Moreover, while the author's studies presented in project two could help target interventions aimed at improving the prevention and/or management of AKI in Wales at where they may have greatest impact, the tool presented in project three could also be used to identify those areas in Wales with most need and/or potential for QI. The work here therefore aligns with a VBHC approach.

An additional and broader practical discussion point relates to the emerging school of thought that AKI is a marker of multi-organ dysfunction and other acute illness, rather than a condition specifically related to disease of the kidney (Ronco *et al*., 2019; Makris and Spanou, 2016; Nissenson, 1998). Because it has many causes and rarely occurs alone, Sykes *et al*. (2018; 2019) call AKI an 'illness barometer', which can commonly be used as a surrogate for general ill health and other underlying disease. Some therefore recommend AKI as a good potential indicator for state of health and quality of care in general (Harty, 2014; Hawkes 2013; James and Pannu, 2015). This thesis may therefore offer more insight into quality of care and the health of the Welsh population than initially anticipated. While it could therefore be claimed that the data set it has developed has the potential to become an index with which to benchmark quality of healthcare provision in Wales more generally, not just that for AKI, this thesis nonetheless confirms AKI as a condition associated with a large cohort of deteriorating patients with poor outcomes. Therefore, and regardless of what its pathophysiology may or may not represent, AKI clearly warrants an obvious focus for measurement and QI.

Whilst this thesis may have numerous 'real-world' implications, the author suggests it also makes a significant contribution to the literature to which it relates. While at the outset of this research, numerous studies had described AKI that is developed during hospitalisation, less had focussed on AKI that is developed in the community. By utilising the novel data set developed by the author in project one, and therefore data on all AKI events occurring in the entire Welsh population, including that in the hospital and community setting, the 11 publications presented in project two include some of the first national, multicentre, and population-based studies to comprehensively describe AKI and its associated factors. The author therefore proposes that in helping better understand the epidemiology of AKI, they significantly add to the AKI epidemiology literature and are likely of interest beyond just Wales.

The author at the same time acknowledges work taken place elsewhere since publication of the author's forementioned studies, including the 2020 published UK Renal Registry 'AKI in England' report. While this report used methods similar to those applied here, it did not include

data collected from all laboratories in England and therefore does not represent a complete country-wide depiction of population AKI (UKRR, 2020). The published works presented as part of this thesis therefore remain, to the author's knowledge, the only true nationwide, population-based characterisations of AKI known to date.

While these studies provide numerous important conclusions, all of which are documented and discussed in project two itself, the author suggests a mainstay of these includes an incidence of AKI in the general adult population that is seemingly higher than previously reported (577 per 100,000 population per year), with almost half (49.3%) of which acquired in the community. Other key findings include the identification that this AKI incidence is more common in elderly patients and patients with pre-existing CKD (with 42.0% of all AKI occurring in the context of pre-existing CKD). Another is its association with significantly poor outcomes which include but are not limited to a one in four risk of death within 90 days (25.6% 90-day mortality rate following all AKI, 30.1% following HA-AKI, and 22.3% following CA-AKI), and for surviving patients, a 1 in 5 chance of developing de-novo CKD (20.5%) or an almost 1 in 2 chance of experiencing progression of pre-existing CKD (45.6%).

While there are many implications to be drawn from the conclusions of these studies, they first corroborate the previously described literature which suggests AKI is becoming more prevalent. They also support the notion that while this may in part be explained by greater reporting resulting from advances in testing technologies and a new internationally agreed consensus definition, it is likely being driven by an ageing and increasingly comorbid population (Horton and Berman, 2015; Xue *et al*., 2006; Hsu *et al*., 2007). Another insightful conclusion includes the observation that AKI presents across the entire health and social care system and commonly occurs in the community. By verifying smaller studies in the literature which have also found CA-AKI to account for a significant proportion of all AKI, this thesis therefore supports the view that AKI represents a problem belonging to the whole healthcare system, not just secondary care and/or the nephrology department.

As an aside, the described studies also clearly demonstrate the burden of AKI. They should therefore strengthen existing calls to the healthcare sector to prioritise improvement in the prevention and management of AKI and could be used to stimulate investment in the development of further innovative QI strategies aimed at achievement of this goal. In addition, by exploring the association of a number of factors with variation in its incidence, the same studies also have potential to inform the development and validation of so-called 'AKI risk-calculator tools', to predict risk of the condition in the general population, and therefore improve its prevention in those at high risk.

The author's studies presented in project three should meanwhile help clinicians better understand the significance of alerts transmitted by electronic AKI alerting systems such as that applied in this thesis; a worthwhile aim given Chang *et al*. (2011) report the acceptance of such a system relies on the end-user's confidence in its likely benefit for care and diminishes over time. From a wider perspective, the same studies could help allay any speculation (Sutton *et al.*, 2020) healthcare providers and professionals in other areas may have regarding the clinical utility and value of such systems and therefore encourage their adoption elsewhere.

From a final theoretical standpoint, while the potential of big data analytics for healthcare may be well documented (Raghupathi and Raghupathi, 2014), this thesis adds to the ever growing body of literature on healthcare informatics and the general discussion regarding its importance for improving care. The author suggests it also highlights the importance and potential benefits of data sets which span the entire healthcare system for researching and better understanding the epidemiology of a condition. Moreover, and specifically for AKI, the author suggests the work here builds on work like that by Sawhney and Fraser (2017), and adds to the conversation concerning the emerging role of large databases in determining the incidence and prognosis of AKI and evaluating initiatives to improve the quality of care related to AKI.

## 1.10 Limitations

As with all research, the conclusions and implications of this thesis must be qualified by its limitations. The author categorises these as those related to the AKI alerting system which it has applied, those related to the availability of and access to data, and those related to the wider and earlier discussed theoretical concept of continuous quality improvement (CQI).

Although it is endorsed by the universally agreed KDIGO (2012) definition of AKI, SCr can be insensitive to rapid changes in GFR and a number of physiological factors can affect its measurement, including age, race, sex, diet, muscle mass, medication, and hydration status. There therefore remains some speculation regarding its precision as a biomarker of renal function (Makris and Spanou, 2016; Basile *et al*., 2012; Edelstein, 2008; Gaudio *et al*., 1982). The laboratory-based system applied in this work is also limited in that it does not include the analysis of urine output, which KDIGO recommend using in conjunction with SCr to identify AKI. An additional drawback of the system and therefore the data set developed in this thesis is any patient presenting with AKI but without a measurement of SCr in the previous 365 days is not included. Because the AKI alerting system described in this thesis is information technology driven and lacks linkage to other data sets, it also lacks intelligence and does not apply any clinical context. For this reason, its algorithm has the potential to inappropriately trigger alerts following the

misclassification of some increases in SCr as AKI, including fluctuations in a patient's SCr concentration due to renal replacement therapy (RRT) and/or pregnancy. While the data cleansing work documented in project one provides some data quality assurance, an ideal system would identify such patients through linkage with other databases. Davies *et al*. (2020) suggest linking the AKI alerting system described in this thesis with routinely collected dialysis timeline and treatment data could reduce the number of so-called false positive alerts issued for patients who are undergoing or recently undergone RRT by almost 20%. While beyond the scope of this thesis, their study nonetheless highlights the limitation of an automated laboratory-based system to accurately identify AKI, and underlines the need for linkage with other data to improve the diagnostic accuracy of such systems.

Ethical approval obtained for the work here was such that it limited the data items that could be collected from the WLIMS and restricted access to other clinical data sets. Richer data sets, including for example information on patient comorbidity, cause of AKI, need for RRT, cause of death, and hospital episode statistics may have offered a more thorough epidemiological exploration of AKI than that presented. References to the Welsh population made in this thesis also exclude the small number of Welsh residents who live close to, and may therefore access healthcare services over, the border. The varying AKI incidence rates reported in this work could also in part have been influenced by differences in frequency of SCr testing, which could be identified through further analysis. The outcomes observed in the 14 studies presented may also have been influenced by the transmission of the alert itself, thus making it difficult to directly compare this work with those studies in the literature which have not used similar methods to identify their sample.

While a strong proposal is made for the potential of the data set presented in this thesis for QI, the author simultaneously acknowledges the notion of CQI philosophy which states measurement is just one of many elements in the QI process. CQI says successful QI relies not only on timely and reliable information, which this thesis enables for AKI, but on wider system factors also. Anderson *et al*. (1994) suggest while robust measurement is important, sustained improvement requires a systems based approach involving behaviour change and commitment from the entire organisation. Tsang *et al*. (2021) recently described the effects of a computerised audit and feedback dashboard for AKI to improve patient safety and concluded that while measurement using information technology can facilitate improvement, other factors require consideration for real improvements in practice to embed. Though these other elements are noteworthy, they have not been the focus of this thesis, which instead has concentrated on the role of measurement in the QI process. While the author therefore accepts that simply measuring something will not automatically improve it, the value of data for instigating change remains well understood (Deming, 1986; Drucker, 1997; Palmer 1998). The author therefore maintains the view that the

new national source of 'fit for use' data presented in this thesis provides a unique opportunity to inform and improve care for patients who develop and/or are at risk of, AKI.

The author also acknowledges the literature which suggests the indicators presented in project three of the thesis should be considered only as starting points for further analysis and investigation. While Campbell *et al*. (2002) suggest quality of care indicators do not provide definitive answers and instead signify potentially unacceptable variation in care, Ellis (2006) argues QI is not only the comparison of performance to identify disparities, but also involves the analysis of processes and factors associated with varying levels of performance. This follows the seminal stance of Donabedian (1966), that the reason for success or failure is generally not identified in the recording of an outcome. Moreover, for most health indicators, there are often many reasons for variation, which may or may not be modifiable. For this reason, variation does not always necessarily imply poor quality of care. The author therefore accepts that the AKI quality indicators developed in this work are not without limitations and are instead offered as precursors for further analysis and investigation. This could for example involve the development and application of additional indicators and/or the interrogation of additional and more lower level data.

## 1.11 Recommendations for future work

From a practical perspective, the author recommends that the data collection and validation processes developed in project one become fully automated. The data set developed in this thesis currently relies on human input (i.e. the author), to routinely extract, cleanse and analyse data from the WLIMS, an approach which is unsustainable in the long term. At time of writing, and following presentation of the work in this thesis to WG, discussions are ongoing regarding automation and the potential adoption of the data set developed here as a new mandated NHSW minimum data set for AKI. Also being discussed with Digital Health and Care Wales is conversion of the prototype tool developed by the author in project three as a new purpose-built 'real-time' dashboard for publishing information on healthcare provision related to AKI, to join similar disease management tools already in use for monitoring and improving care across the principality. Regardless of this work being taken forward however, Campbell *et al*. (2002) suggest the interpretation and usage of data on healthcare quality is a political and resource issue rather than a methodological or conceptual one. It is therefore likely the practical implementation of the work presented in this thesis remains a question that is beyond the author's influence.

From a research perspective, the author suggests the epidemiological studies presented in the thesis potentially may not utilise the data set they apply to its full potential. Through further

multivariate analysis of variables available in these data and/or linking with other data, future work could explore the association of comorbidities, mental health and other acute illnesses with the prevalence of AKI, or the relationship between medicines management and AKI incidence and outcome, and could help further understand the epidemiology and aetiology of AKI. Moreover, although some studies presented in this thesis have collected data on the development and progression of CKD following AKI, these were limited by post AKI follow-up data of 90 days. Longer-term studies of follow-up are therefore needed to truly describe the association of AKI with CKD.

While some meta-analyses (Lachance *et al*., 2016; Sutton *et al,* 2020; Zhao *et al.,* 2021) have successfully demonstrated the benefits of AKI e-alerts, a number of recent studies doubt their utility for improving care and outcomes for patients diagnosed with AKI (Wilson *et al*., 2021; Baird *et al*., 2021; West Midlands Acute Medicine Collaborative, 2019). Abandonment of CDSSs for AKI based on the premature data available would however be controversial. By building on the author's study presented in project three, future work could use the data set developed in this thesis to robustly evaluate the efficacy of CDSSs as interventions for improving care of AKI, and explore how far, and to what extent, they alter clinician behaviour. Moreover, given research on quality indicators in the field of AKI is limited, future work could build on the indicators put forward by the author in this thesis and follow work like that of Kashani *et al*. (2019). The author suggests that from a wider perspective, the methods employed to develop the indicators here could also contribute to discussions regarding the earlier described calls from the OECD (2017), for better benchmarking of quality between UK care providers.

While the work here has centred on the utility of routine SCr data for epidemiological research and quality improvement in care for AKI, the author also presents the work as a wider proof of concept which could be applied elsewhere. The work here is not only transferrable to healthcare systems out with Wales, it is also applicable to other common preventable and/or reversible health conditions which are not necessarily acute or related to the kidney but which like AKI, are identifiable by biomarkers. Whereas this thesis has involved using SCr as a biomarker for AKI and often potential subsequent CKD, there are a number of other routinely undertaken laboratory-based diagnostic tests to which the author anticipates an approach similar to that presented here could be applied. For instance, given non-alcoholic fatty liver disease (NAFLD) is speculated as the next potential pandemic (Lazarus, 2020), this could involve utilising data on aspartate aminotransferase (AST) and aminotransferases alanine aminotransferase (ALT) ratios, which is used to identify suspected liver fibrosis and which can lead to chronic liver disease. Other examples include Haemoglobin A1c (HbA1c), which is used to identify potential diabetes mellitus and, brain natriuretic peptide (BNP) and/or N-terminal pro b-type natriuretic peptide (NT-proBNP), which is used to identify potential heart failure. Replicating the concept presented

by the author in this thesis for these other routine population healthcare data could help better understand the epidemiology of, and inform improvement in the prevention and management of, the conditions to which they relate.

## 1.12 Contribution to knowledge

The original contribution to knowledge is:

(i) The methodological development of a new validated nationwide data source for AKI, which enables the reliable identification of all AKI occurring in the entire population of the country of Wales, including that which is hospital and community acquired.

(ii) The application of the aforementioned novel data set to provide the first comprehensive population-based epidemiological description of AKI.

(iii) The application of the aforementioned novel data set to demonstrate, and identify potential opportunities to further refine, the clinical utility of electronic AKI alerting systems.

(iv) The development of a prototype of a tool which, in utilising the aforementioned novel data set, SPC methods, and quality indicators developed by the author, provides an innovative means to robustly measure, monitor and compare rates of AKI incidence and AKI associated mortality across all of Wales, a mechanism which did not exist prior.

This, to the author's knowledge, is work not achieved on this scale before. As validation of this original contribution, the peer-reviewed status of the author's 14 published works presented throughout the thesis are also offered. Published as 'open access' in peer-reviewed journals during the five year period of 2016 to 2021, according to the ISI Web of Science, these articles have accumulated a total of 209 citations to date (Accessed 16 February 2022). To increase their dissemination further, and to maximise engagement with fellow researchers, abstracts of the work have also been presented to a number of academic societies and other learned forums, including at national and international meetings (Appendix 1.3).

## 1.13 Contributions of the author

This thesis was written entirely by the author (JH) with editorial support from her supervisory team. This included Dr Ray Higginson as Director of Studies, and Professor Aled O. Phillips (AOP) and Professor John Geen (JG) as clinical supervisors and who also set up the national AKI work programme to which the thesis relates. The peer-reviewed studies presented in projects two and three were written on behalf of the national AKI Steering Group, to which JH was employed as the full time data analyst. Of the 14 published works presented, JH first authored 10 and for which JH was responsible for co-designing the studies, collecting and analysing the data, producing the tables and figures, and co-writing the manuscripts. For the 4 studies not first authored by JH, JH was responsible for co-designing the studies, collecting the data, supervising the first author in analysing the data, and co-writing the manuscripts. For all studies, AOP and JG set out the hypotheses, interpreted the results, and co-wrote the manuscripts. For work documented in project one, JH received support from the following colleagues. The data collection process was conceived by JH with support from Mr Stephen Winder and Dr Alan Dodd. The clinical audit was completed by JH with support from Miss Gina Sanki. For work documented in project three, JH developed and designed the prototype tool under direction of AOP and JG.

## 1.14 Personal reflection of the author

Before reflecting on lessons learnt and potential areas for improvement, there are a number of aspects I feel went well during my period of study. The first is a practical one and relates to the papers written prior and alongside writing the thesis. Writing these papers progressed my academic writing skills substantially, and at pace, and likely made the thesis writing process easier than I may have found it without such writing experience. Also helping me in my research and write up process were the number of positive behaviours I adopted throughout, including practicing good time management, realistic goal setting, and taking a disciplined and organisational approach to note-taking, reading and referencing. Another was the thinking time I allowed myself which, although could be considered time not spent necessarily ‘producing’, resulted in some of my most pivotal thoughts and connections. From my experience, some of the most radical ideas and so-called ‘lightbulb moments’ often materialise during times and in situations you least expect, not always at a desk. Journaling has meanwhile enabled me to reflect on how far my thinking has travelled throughout the study process. Documenting my progress in this way has been particularly helpful during difficult periods and if I was to restart, I would start this activity earlier.

While many aspects may have gone well, numerous challenges have also been encountered and there are some things which on reflection I may have done differently. The first is a practical one and relates to a recommendation made above and project one of the thesis. Earlier investment in learning more advanced programming languages and softwares may have resulted in faster data processing and analysis times and therefore simplified the undertaking of some of the later work that is documented. I also likely had a number of unrealistic expectations when entering this PhD process. This included my naivety regarding research ethics and the difficulties in accessing additional data. I also underestimated how demanding the write-up process would be, academically, personally and in terms of time. In hindsight, I was also late to acknowledge that a doctoral project evolves over time and as it is written, and the content planned at the beginning is often different to what is produced at the end.

My final reflection is the value of support from others. At first I may have mistakenly viewed this thesis as a solo effort and while a large proportion of the work has been such, being able to lean on others for input and feedback has been critical for me not only completing but maintaining perspective during. I am especially grateful for the relationships with my supervisors, who have guided me throughout the entire process and from whom I have learnt so much.

There are a number of lessons I take from this research process, and not only as a researcher. One relates to being told that this thesis is not my life's work, but rather a starting point. This resonating statement helped me accept that this thesis would not and could not be perfect, something I perhaps wish I'd realised sooner. It was also quite empowering to realise this doctorate as the beginning of my research career, and not the end. Emerson (1844) famously wrote success is not about the destination, but the journey itself. I now understand and appreciate the 'PhD' as a journey, a long, non-linear process which is supposed to challenge, and which involves failures as well as successes. I have learnt and grown during this PhD experience and end it more resilient and better equipped for future research endeavours.

# Chapter 2: Project 1

## Development and validation of a national data set for AKI

### 2.1 Introduction

As set out in chapter one, in the quality literature, Deming (1986) describes quality as 'fitness for use'. In the context of data, data quality translates to data that are fit for use by data consumers and which can meet their specific goals. If data on AKI alerts triggered by the Welsh AKI alerting system were to be used for epidemiological research in AKI and/or inform improvement in healthcare provision related to AKI, it was therefore important that first, processes for generating these large data sets were developed, and second, these data were 'fit for use'. Quality assuring these data was essential if they were to be suitable for analysis and application. By applying the Welsh AKI alerting system as a centralised system of data collection, this first project of the portfolio style thesis describes work undertaken by the author to systematically and reliably collect, and quality assure, national data on AKI alerts. It also documents work undertaken by the author to develop a method which could be used to, automatically, using the data, classify the clinical setting of alerts, as either hospital acquired (HA) or community acquired (CA) AKI. Finally, not all AKI alerts can be assumed to represent a distinct clinical episode of AKI. The work here also therefore includes the development of a method by the author which could be used to automatically, using the data, distinguish between AKI alerts and incident episodes of AKI.

### 2.2 Aims and objectives

In addressing the first aim of the thesis, the aim of this project was to develop a validated national data set for AKI. To achieve this aim, the objectives were as follows:

1. Develop processes to extract data on AKI alerts.
2. Develop processes to cleanse data on AKI alerts.
3. Develop a method to classify the clinical setting of AKI alerts.
4. Develop a method to distinguish between AKI alerts and AKI episodes.

## 2.3 Extraction and cleansing of data

### 2.3.1 Development of processes to extract data on AKI alerts

As described in chapter one, the AKI alerting system applied in this thesis is based in the Welsh Laboratory Information Management System (WLIMS), an 'InterSystems TrakCare Lab' database, which all 19 laboratories in NHSW use for the administration of test results, including serum creatinine (SCr). From the time of its activation in the WLIMS, it is therefore possible for the previously described national AKI alert algorithm (Figure 1.3) to be applied to collect data on all AKI events occurring in the entire population of Wales, in all care settings.

To extract data on patients for which an AKI alert had been triggered, the web-based 'InterSystems TrakCare DeepSee' software platform was employed, with each row of data representing a SCr result. This thesis is based on the collection of all SCr results, and therefore all AKI alerts, for the period of November 2013 to March 2019. This data was collected by the author over time and as a series of separate monthly files. Due to the volume of data requiring extraction each time, the collection process involved a number of steps. While ideally the relevant data would have been extracted in a single step, this involved a complex query with nested subqueries that was too cumbersome for the forementioned 'DeepSee' application to process. Despite efforts to streamline this query, the method illustrated in Figure 2.1 was selected as the more practicable and reliable approach.

**Data collected from the WLIMS**

Table 2.1 lists the items included in each raw data extraction from the WLIMS. In addition to the SCr result value, this included information on patient demographics and the test location related to each result. For SCr results associated with an AKI alert, information on the alert was also extracted, including the baseline SCr, the AKI alert code, the AKI stage, and which of the three algorithm rules was responsible for triggering the alert.

**Data collected from other sources**

To enable more reliable data, some data items were collected from sources other than the WLIMS, including data on mortality and place of residence. Whilst initially collected from the WLIMS, a high proportion of cases were found to have a date of death field incorrectly populated and/or missing data. The date of death field in the WLIMS is linked to a separate database called the Welsh Demographic Service (WDS) and a temporary error in this link was suspected to be causing this problem. To overcome this issue, data on date of death was therefore alternatively collected

from source (WDS) using batch tracing methods. This involved using NHS number to link the two datasets and uploading lists of NHS numbers drawn from the WLIMS extracted data to the NHS Wales Informatics Service data warehouse which hosts WDS. Each upload, on average, achieved a 99.0% overall match rate. Data on patient postcode and lower super output area (LSOA) of residence was also collected from WDS. This enabled cross-referencing with the Welsh Index for Multiple Deprivation (WIMD), Welsh Government's official measure of relative deprivation, which ranks the 1909 geographical areas (LSOAs) in Wales on the basis of eight domains; income, employment, health, education, access to services, community safety, physical environment, and housing (WIMD, 2014). Using the patient postcode, 97.5% of patients were successfully georeferenced to a LSOA of residence and WIMD rank. Possible reasons for failed matches included input errors at source and/or patient records which had not been updated for some time and therefore contained postcodes which were now classified as inactive.

**Calculated data fields**

The recording and coding of test locations in the WLIMS is such that the first three and five characters of a location code refers to the associated organisation and site respectively (Table 2.2). The NHS Wales organisation field was therefore derived using the VLOOKUP function in Microsoft Excel and based on the first three characters of the location code field. Using the same method, the NHS Wales site field was derived based on the first five characters of the location code field.

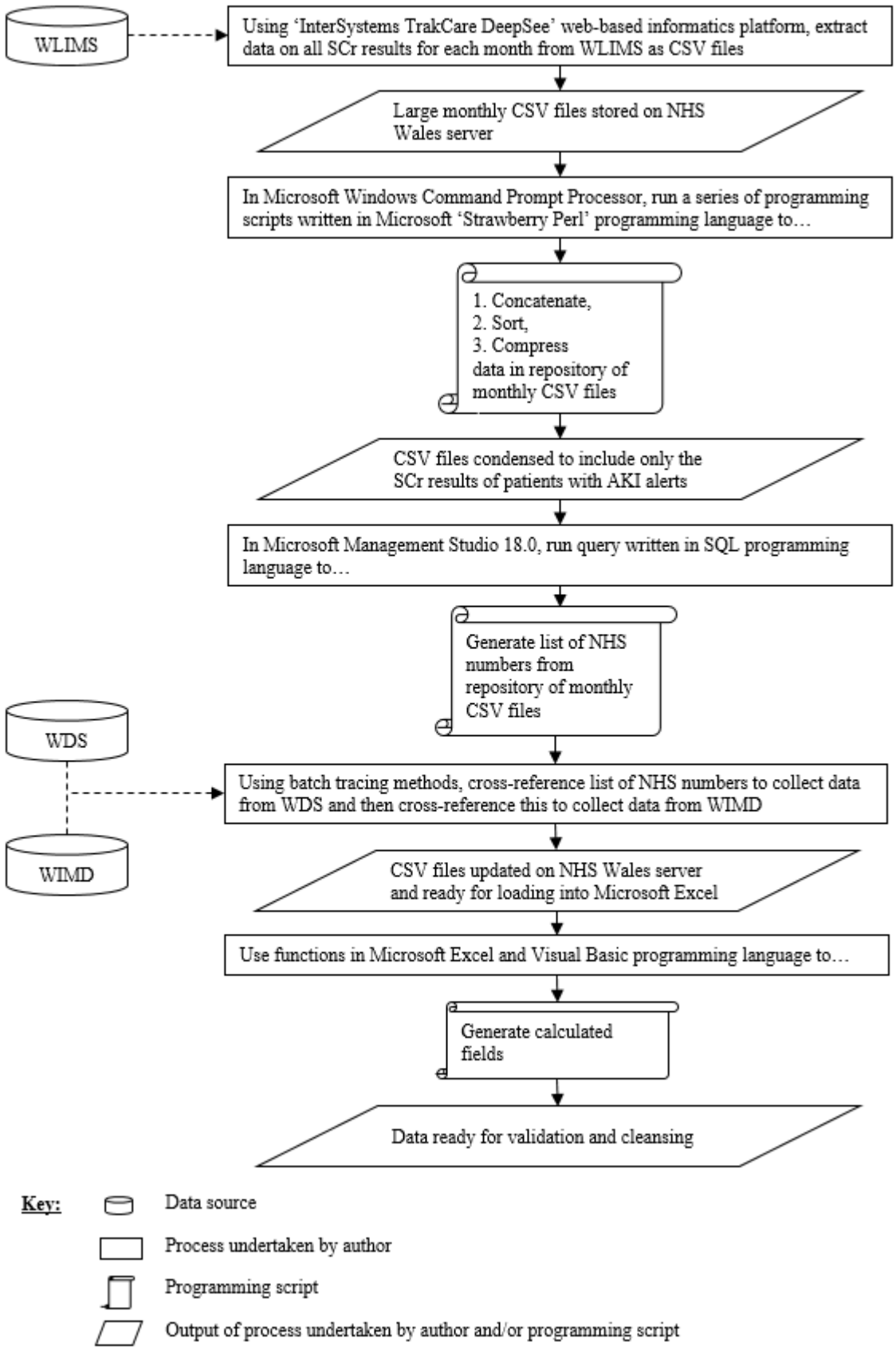



**Figure 2.1:** Process developed by the author to extract raw data on AKI alerts from the WLIMS. *CSV, Comma-separated values (a text file format).*

**Table 2.1:** List of fields included in national AKI data set developed by the author

| Field | Source |
|---|---|
| NHS number | WLIMS |
| Gender | WLIMS |
| Date of birth | WLIMS |
| Age | WLIMS |
| Result date | WLIMS |
| SCr value | WLIMS |
| RV1 | WLIMS |
| RV2 | WLIMS |
| RV ratio | WLIMS |
| Baseline SCr | WLIMS |
| AKI alert code | WLIMS |
| AKI stage | WLIMS |
| AKI rule | WLIMS |
| Location code | WLIMS |
| Location description | WLIMS |
| Patient type code | WLIMS |
| Patient type description | WLIMS |
| Clinical specialty code | WLIMS |
| Clinical specialty description | WLIMS |
| Postcode | WDS |
| Date of death | WDS |
| LSOA | WDS |
| WIMD rank | WIMD |
| NHS Wales organisation | Calculated |
| NHS Wales site | Calculated |

**Table 2.2:** Location codes associated with test location in the WLIMS

| Organisation code | Organisation | Site code | Site |
|---|---|---|---|
| 7A1 | Betsi Cadwaldr University Health Board | 7A1A1 | Ysbyty Glan Clwyd |
| | | 7A1A4 | Wrexham Maelor |
| | | 7A1AU | Ysbyty Gwynedd |
| | | 7A1AV | Llandudno |
| 7A2 | Hywel Dda University Health Board | 7A2AG | Ysbyty Glangwili |
| | | 7A2AJ | Bronglais Hospital |
| | | 7A2AL | Llanelli |
| | | 7A2BL | Withybush Hospital |
| 7A3 | Swansea Bay University Health Board | 7A3B7 | Princess of Wales |
| | | 7A3C4 | Singleton |
| | | 7A3C7 | Morriston |
| | | 7A3CJ | Neath Port Talbot |
| 7A4 | Cardiff and Vale University Health Board | 7A4BV | University Hospital of Wales |
| | | 7A4C1 | University Hospital Llandough |
| | | 7A4C3 | Dental School UHW |
| 7A5 | Cwm Taf Morgannwg University Health Board | 7A5B1 | Royal Glamorgan |
| | | 7A5B3 | Prince Charles |
| 7A6 | Aneurin Bevan University Health Board | 7A6AM | Nevill Hall |
| | | 7A6AR | Royal Gwent |
| | | 7A6AV | Ysbyty Ystrad Fawr |
| RQF | Velindre NHS Trust | RQF5B | Welsh Blood Service |
| | | RQFH5 | Velindre |

### 2.3.2 Development of processes to cleanse data on AKI alerts

While the inevitability of missing and/or unreliable healthcare data is well documented (Sterne *et al*., 2009), the risk that these data may pose for research and practice can be overcome through various computational methods. For the SCr data described above to be considered suitable for analysis, processes to cleanse these raw data were also required.

**Missing and/or invalid data**

Using the extraction method described in Figure 2.1, a test data set was generated by the author. This included data on 31,601 alerts triggered for 17,689 patients aged 18 years or older during the six month period of March to August 2015. Formulas in Microsoft Excel were then developed to check for missing data and/or errors in the type and format of these data. This included screening, and checking for invalid entries in, the following fields:

- SCr value (as defined by blank or not numeric data type),
- NHS number (as defined by blank or not equalling 10 digits),
- Gender (as defined by not 'M' or 'F'),
- Date of birth (as defined by blank or > Result date or <> 'dd/mm/yyyy'),
- Date of death (as defined by blank or < Result date or <> 'dd/mm/yyyy'),
- Location code (as defined by blank or 'Unknown')

Results revealed 0.1% of SCr results in the test data set were missing or contained an invalid SCr value and could therefore be described as not suitable for analysis. For example, this included a number of rows with a SCr value of 'H', referring to a haemolysed sample, and 'L', referring to a lipemic sample. 0.1% of SCr results were meanwhile missing or containing an invalid NHS number, <0.1% were missing or containing an invalid entry in the gender field, <0.1% were missing or containing an invalid date of birth, <0.1% contained an invalid date of death, and <0.1% related to an unknown location.

**Inappropriate AKI alerts**

While the rules above enabled missing and/or invalid data to be identified and therefore excluded from raw data collected from the WLIMS, also required were processes to cleanse these initially extracted data of those AKI alerts unsuitable for analysis because they unlikely represent actual AKI. This first included identifying 'SAKI' coded alerts, which as described in chapter one, do not represent a diagnosis of AKI based on the KDIGO definition of AKI. Secondly, the national AKI alert algorithm had the potential to inappropriately trigger alerts following misclassification

of some increases in SCr as AKI, including fluctuations in a patient's SCr concentration due to renal replacement therapy (RRT) and fluctuations in a patient's SCr concentration due to pregnancy. Processes were therefore required to identify, using the data, those alerts inappropriately triggered for patients who, at time of alerting, were undergoing and/or had recently undergone RRT, and patients who, at time of alerting, were pre- or post-partum.

**Identification of 'SAKI' alerts:** Using the same test data set as above, 14.5% of alerts were 'SAKI' alerts and therefore did not represent actual AKI based on the KDIGO definition of AKI. Such alerts could easily be identified and therefore excluded from raw data extracted from the WLIMS using the 'AKI alert code' field.

**Identification of inappropriate alerts related to pregnancy:** 4.2% of alerts were triggered by a measurement of SCr in an 'Ante-natal' coded location (Table 2.3). This suggests that rather than actual AKI, these alerts likely represent increases in a patient's SCr concentration towards pre-pregnancy concentrations post-partum. Such alerts could easily be identified and therefore excluded from raw data extracted from the WLIMS using the 'Patient type code' field.

**Identification of inappropriate alerts related to RRT:** While the 'Patient type code' field could be used to identify a large proportion of those alerts inappropriately triggered for patients undergoing, or having recently undergone, RRT (as indicated by a measurement of SCr in an 'Dialysis', 'Renal' and 'Renal and Transplant' coded location) an audit was also conducted to investigate if particular alert codes (Table 1.3) and/or conditions are frequently associated with this patient cohort.

From the same test data set described above, a sample including 200 alerting patients distributed across two health boards (Cardiff & Vale University Heath Board and Aneurin Bevan University Health Board) and all nine alert codes was generated. Using NHS number as the patient identifier to cross reference, local hospital patient management systems and the Welsh national renal patient database (VitalData) were used to identify whether patients were known to be on RRT at the time of alerting. Results showed only three of the nine alert codes (ABS1, DELTA1, and ABS2) were associated with patients known to be on RRT at time of alerting. While 89% of patients triggering ABS1 alerts were on RRT at time of alerting, this value was 60% for patients triggering DELTA1 alerts with SCr values greater than 400 µmol/L and 26% for patients triggering ABS2 alerts. These results suggest that rather than actual AKI, a high proportion of ABS1 and DELTA1 alerts likely represent fluctuations in a patient's SCr concentration due to RRT and may therefore not be suitable for analysis. Such alerts could easily be identified and therefore excluded from raw data extracted from WLIMS using the 'AKI alert code' and 'SCr value' fields. Discounting these alerts would also however risk the exclusion of a small number of patients with actual AKI.

Given the 89% error rate and 105 of the 17,689 patients in the test data set were flagged by ABS1, excluding these alerts equates to, on average:

> excluding 0.07% ((11%*105)/17,689) of patients identified with the algorithm with probable AKI. Their inclusion meanwhile risked, on average, including 0.53% ((89%*105)/17,689) of patients identified by the algorithm who are likely on RRT, and alerts which therefore likely represent probable false cases of AKI.

Given the 60% error rate and 89 of the 17,689 patients in the test data set were flagged by DELTA1 and SCr values greater than 400 µmol/L, excluding alerts meeting these criteria equates to, on average:

> excluding 0.20% ((40%*89)/17,689) of patients identified by the algorithm with probable AKI. Their inclusion meanwhile risked, on average, including 0.30% ((60%*105)/17,689) of patients identified by the algorithm who are likely on RRT, and alerts which therefore likely represent probable false cases of AKI.

In contrast, given the lower 26% error rate seen in ABS2 alerts, and 562 patients in the test data set were flagged by this code, excluding these alerts equates to, on average:

> excluding 2.35% ((74%*562)/17,689) of patients identified by the algorithm with probable AKI. Their inclusion meanwhile risked, on average, including 0.83% ((26%*562)/17,689) of patients identified by the algorithm who are likely on RRT, and alerts which therefore likely represent probable false cases of AKI.

From the results described, it could be concluded that:

- While ABS1 alerts may in a small number some cases represent actual AKI, a large proportion likely represent false cases AKI, and are inappropriately triggered by the algorithm following the misclassification of fluctuations in a patient's SCr concentration due to RRT. Such alerts should therefore be considered unsuitable for analysis and their exclusion from raw data extracted from the WLIMS necessary.
- While DELTA1 alerts triggered by SCr values greater than 400 µmol/L may in a small number of some cases represent actual AKI, a large proportion likely represent false cases of AKI, and are inappropriately triggered by the algorithm following the misclassification of fluctuations in a patient's SCr concentration due to RRT. Such alerts should therefore

be considered unsuitable for analysis and their exclusion from raw data extracted from the WLIMS necessary.

- While ABS2 alerts may in a small number of cases represent probable false cases of AKI, and are inappropriately triggered by the algorithm following the misclassification of fluctuations in a patient's SCr concentration due to RRT, a large proportion likely represent actual AKI. Such alerts should therefore be considered suitable for analysis and their exclusion from raw data extracted from the WLIMS not necessary.

**Inclusion and exclusion criteria for national AKI data set**

In collating all of the results described above, Table 2.4 refers to the template of formulas developed by the author in Microsoft Excel, designed to be applied to raw data on AKI alerts extracted from the WLIMS immediately following the process outlined in Figure 2.1.

**Table 2.3:** Patient type codes and descriptions associated with test location in the WLIMS

| Patient type code | Patient type description |
|---|---|
| AE | Accident & Emergency |
| AN | Ante-natal |
| COM | Community |
| COR | Coroner |
| DC | Day Case |
| DEN | Dental |
| DIAL | Dialysis |
| ENV | Environmental |
| FD | Funeral Director |
| FOR | Forensic |
| FP | Family Planning |
| GP | GP Practice |
| GUM | Genito-Urinary Medicine |
| HO | Home Office |
| IND | Industrial |
| IP | Inpatient |
| ITU | ITU and High Dependency |
| NON | Non-Biological |
| OH | Occupational Health |
| OP | Out Patient |
| ORT | Outpatient rapid turnaround |
| OTH | Other |
| PM | Post Mortem |
| PP | Private Patient |
| RAT | Renal and Transplant |
| RD | Research and Development |
| REN | Renal |

**Table 2.4:** Inclusion and exclusion criteria for national AKI data set developed by the author. *Data fields indicated by italics.*

| **Exclude from data set if:** |
|---|
| **1.** *SCr value* is invalid (as defined by blank or not numeric data type),<br>**2.** *NHS number* is invalid (as defined by blank or not equalling 10 digits),<br>**3.** *Gender* is invalid (as defined by not 'M' or 'F'),<br>**4.** *Date of birth* is invalid (as defined by blank or later than date of SCr result and/or not formatted as 'dd/mm/yyyy'),<br>**5.** *Date of death* is invalid (as defined by earlier than date of SCr result and/or not formatted as 'dd/mm/yyyy'),<br>**6.** *Location code* is invalid (as defined by blank or 'Unknown'),<br>**7.** *Alert code* is 'SAKI',<br>**8.** *Patient type description* is 'Ante-natal', 'Renal Dialysis', 'Renal', or 'Renal and Transplant',<br>**9.** *Alert code* is 'ABS1', or<br>**10.** *Alert code* is 'DELTA1' and *SCr value* > 400 µmol/L. |

## 2.4 Classification and analysis of data

### 2.4.1 Development of a method to classify the clinical setting of AKI alerts

While only few studies in the literature at the outset of this thesis had analysed AKI that is acquired in the community, it is likely that HA- and CA-AKI represent different patient cohorts requiring different management strategies. If the data set developed by the author here was to inform the epidemiology of AKI and inform improvement in healthcare provision related to AKI, it was therefore important to be able to, in the data, distinguish between these two cohorts. While the classification of alerts as such would ideally involve linkage with national hospital admission data, access to such data was not possible. A method which could be used to automatically, using the SCr test location associated with alerts, was therefore required to classify the clinical setting of alerts. Using formulas in Microsoft Excel and the previously described 'Patient type code' field, six different versions of such a method were developed (V1-V6) (Table 2.5). While all include classifications for HA- and CA-AKI, V4-V6 can also categorise alerts as 'Not AKI' and 'Undetermined'. Each method could also sub-classify CA-AKI and identify those alerts triggered in a primary care setting (as indicated by a 'GP' (General practice) patient type code).

Using the previously described test data set, a sample including 160 alerting patients at Prince Charles Hospital, located in Merthyr Tydfil, in Cwm Taf Morgannwg University Health Board was generated. To identify the most accurate method, the six different methods were applied to the sample and results were compared with the actual clinical setting of alerts. Using the NHS number as the patient identifier to cross reference, alerts were identified as 'actually' HA or CA using hospital admission data accessed via the local hospital patient management system and by manually reviewing the biochemical history of the 160 patients. To identify any potential false cases of AKI, the local hospital patient management system was used to identify whether patients were pregnant at the time of alerting, and the Welsh national renal patient database (VitalData) was used to identify whether patients were known to be undergoing RRT at the time of alerting.

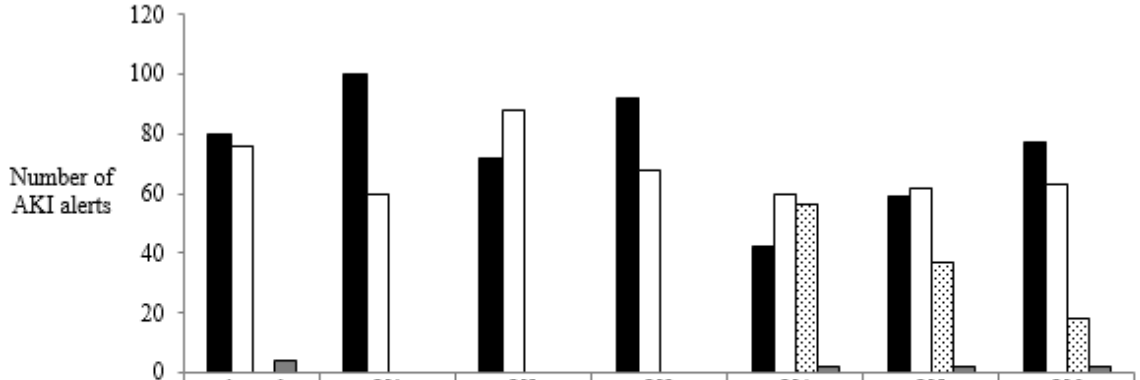
Of the 160 cases reviewed, 80 (50%) were acquired during an inpatient stay and were therefore HA-AKI, and 4 (3%) did not represent actual AKI, including two alerts triggered for patients who were pregnant at time of alerting, and two alerts triggered for patients known to be on dialysis at time of alerting. The remaining 76 (48%) cases were therefore CA-AKI. Whereas methods V1 and V3 overestimated the incidence of HA-AKI by 25% and 15% respectively, V2, V4, V5 and V6 underestimated the incidence of HA-AKI by 10%, 48%, 26%, and 4% respectively (Figure 2.2). V3 produced the most accurate overestimate of HA-AKI and while from a service planning perspective it may be more appropriate to overestimate rather than underestimate the incidence of HA-AKI, 12 (8%) of the 92 alerts V3 classified as such were patients with a recent in hospital

measurement of SCr but who had since been discharged. These were therefore cases of CA-AKI that V3 had misclassified as HA-AKI. V6 reported the next closest to actual estimate of HA-AKI incidence (77), and while this may be an underestimate, it only failed to correctly classify 3 (4%) of the 80 actual HA-AKI cases and also successfully identified half of the pseudo AKI cases.

From the results described above, it could be concluded that compared to V1-V5, V6, which classifies an alert as HA-AKI if triggered by an inpatient following a measurement of SCr in a hospital setting in the previous seven days, offers the most accurate method for automatically classifying alerts as HA- or CA-AKI. Use of this method to classify the data set developed by the author here could help ensure a reported clinical setting which best represents the actual clinical setting of the AKI.

**Table 2.5:** Different methods developed by the author to classify the clinical setting of AKI alerts

| Version | Clinical setting | Criteria |
|---|---|---|
| V1 | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) |
| | CA-AKI | If not 'HA-AKI' |
| V2 | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr was also received in an inpatient setting |
| | CA-AKI | If not 'HA-AKI' |
| V3 | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr was received in a hospital setting (as defined by IP, ITU, AE, DC, OP, or ORT patient type code) |
| | CA-AKI | If not 'HA-AKI' |
| V4 | Not AKI | If alerting patient received a measurement of SCr in a dialysis setting in the previous 30 days (as defined by DIAL patient type code) |
| | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr was received in a hospital setting and in the previous 48 hours (as defined by IP, ITU, AE, DC, OP, or ORT patient type code) |
| | Undetermined | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr not within the previous 48 hours |
| | CA-AKI | If not 'Not AKI', 'HA-AKI' or 'Undetermined' |
| V5 | Not AKI | If alerting patient received a measurement of SCr in a dialysis setting in the previous 30 days (as defined by DIAL patient type code) |
| | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr was received in a hospital setting and in the previous 72 hours (as defined by IP, ITU, AE, DC, OP, or ORT patient type code) |
| | Undetermined | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr not within the previous 72 hours |
| | CA-AKI | If not 'Not AKI', 'HA-AKI' or 'Undetermined' |
| V6 | Not AKI | If alerting patient received a measurement of SCr in a dialysis setting in the previous 30 days (as defined by DIAL patient type code) |
| | HA-AKI | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr was received in a hospital setting and in the previous 7 days (as defined by IP, ITU, AE, DC, OP, or ORT patient type code) |
| | Undetermined | If alert triggered by measurement of SCr received in an inpatient setting (as defined by IP or ITU patient type code) and if alerting patient's previous measurement of SCr not within the previous 7 days |
| | CA-AKI | If not 'Not AKI', 'HA-AKI' or 'Undetermined' |




| | Actual | V1 | V2 | V3 | V4 | V5 | V6 |
|---|---|---|---|---|---|---|---|
| HA-AKI | 80 | 100 | 72 | 92 | 42 | 59 | 77 |
| CA-AKI | 76 | 60 | 88 | 68 | 60 | 62 | 63 |
| Undetermined | 0 | 0 | 0 | 0 | 56 | 37 | 18 |
| Not AKI | 4 | 0 | 0 | 0 | 2 | 2 | 2 |

**Figure 2.2:** Comparison of different methods developed by the author to classify the clinical setting of AKI alerts

### 2.4.2 Development of a method to distinguish between AKI alerts and AKI episodes

An electronic AKI alert is a laboratory-based diagnosis and only once interpreted in the clinical context can it be confirmed as an actual clinical diagnosis of AKI. Not all alerts triggered by the AKI alerting algorithm described in this thesis can therefore be assumed to represent an actual clinical episode of AKI. To overcome at least some of this issue, the algorithm suppresses unnecessary repeated alerts, defined as those triggered by SCr values <6% greater than the preceding alerting SCr (2*coefficients of the between batch variation for SCr across NHSW laboratories (3%)). Despite this logic however, patients could still trigger multiple alerts in a short time period which in reality could constitute the same incident episode. A method which could be used to automatically, using the data, distinguish between AKI alerts and AKI episodes was therefore required.

To explore common definitions adopted by other researchers in the field, a review of the literature was undertaken. The described search showed the duration of a clinical episode of AKI varies and a time period and/or rule with which to define the end of an episode is difficult to universally and/or automatically define. However, based on international care guidelines for AKI and CKD (NICE, 2013; KDIGO, 2012), which recommend reassessment for the evaluation of future risk at three months following an AKI, and given it had previously been used as a definition by other researchers in the field (Sawhney *et al.,* 2017), discussions by the Welsh AKI steering group, which included clinical representation, concluded:

> *AKI alerts triggered for the same patient within 90 days of a previous alert should be considered part of the existing episode and not be considered a new incident episode of AKI.*

Adoption of this definition when analysing the data set developed by the author here could help ensure a calculated incidence that best represents the actual, or 'true' incidence of AKI.

## 2.5 Summary of project

In addressing the first aim of the thesis, this first project has described work undertaken by the author to develop a validated and 'fit for use' national data set for AKI. This novel data set enables the identification of all AKI diagnosed in the entire Welsh population, including that originating in both the hospital and community setting. A data set with this scale and scope is yet to be proven elsewhere.

By applying the Welsh AKI alerting system as a centralised system of data collection, the work presented here has described the development of processes by the author to systematically and reliably extract national data on AKI alerts from the WLIMS. It has also described the development of processes by the author to cleanse these data, so that they can be considered suitable for analysis. Finally, it has also described work undertaken by the author to develop methods which could be used to automatically classify and analyse these data, so that they can be used to reliably calculate an incidence of HA- and CA-AKI which best reflects the actual clinical incidence of AKI. The work here therefore underpins the remaining work that is documented in the thesis, and also provides the necessary confidence in its presented findings and conclusions.

# Chapter 3: Project 2

## Application of a national data set for epidemiological research in AKI

### 3.1 Introduction

As set out in chapter one, the improvement science literature states that for something to improve, it first must be measured (Deming, 1986; Drucker, 1997). Moreover, at the outset of this research, the epidemiology of AKI was not fully understood. While numerous studies had described AKI that is developed during hospitalisation, less had focused on AKI that is developed in the community. Therefore, if the quality of care for patients who develop and are at risk of AKI was to be improved, it was important that before this, the nature and burden of the condition was first fully understood. This second project of the portfolio style thesis includes a series of peer-reviewed studies by the author which, by applying the data set developed by the author in project one, collectively provide a comprehensive epidemiological description of AKI. The 11 published works presented follow two themes; they either define and describe the incidence and outcome of AKI in a selected patient population and/or healthcare setting, and/or they explore factors associated with variation in the incidence and/or outcome of AKI. Moreover, by utilising the aforementioned novel data set, and therefore data on all AKI events occurring in the entire Welsh population, including that in the hospital and community setting, the publications presented include some of the first national, multicentre, and population-based studies to describe AKI and its associated factors. The author therefore proposes that in helping to better understand the epidemiology of AKI, the work documented here makes a significant contribution to the literature to which it relates, and is likely of interest beyond just Wales.

### 3.2 Aims and objectives

In addressing the second aim of the thesis, the aim of this project was to explore and demonstrate the potential of the national AKI data set developed by the author in project one, for epidemiological research in AKI. To achieve this aim, the objectives of the project were as follows:

1. Define and describe the incidence and outcome of AKI in different patient populations and/or healthcare settings.
2. Explore factors associated with variation in the incidence and/or outcome of AKI.

## 3.3 Methodology

The 11 prospective national cohort studies presented in this project all applied similar quantitative, observational and descriptive methods. While this section gives an overview of the methods employed in each study, more detailed accounts may be found in the publications themselves (Appendix 3.1-3.11).

**Data collection and analysis:** While all studies used data sets developed using processes developed and described by the author in project one of this thesis, the specific cohort creation criteria employed by each individual study are described in the study abstracts that follow in section 3.4. Statistical analysis of the data was conducted in IBM SPSS Statistics Version 23.0 and P values less than 0.05 were considered statistically significant in all studies.

**Time horizon of studies:** The 11 studies presented in this project took place during the period of 2015 to 2020 and were based on AKI alerts triggered by the Welsh AKI alerting system during the period of November 2013 to March 2019. Not all studies were based on the same time period however with sample sizes dependent on when each study was conducted. For example, whereas the first study below (Published work 1) was published in 2016 and included alerts triggered during the six month period of March to August 2015, studies which took place later were based on far larger samples and periods of up to four years.

**Incidence of AKI:** AKI was defined by all studies using electronic AKI alerts triggered by the Welsh AKI alerting system, which, as described in chapter one, are based on changes in SCr in accordance with internationally agreed KDIGO definition for AKI. The studies defined an incident episode of AKI as 90 days, using the method developed by the author in project one. Per population incidence rates were calculated using Office for National Statistics mid-year population estimates (ONS, 2016; 2017; 2018; 2019) and since studies were conducted at different timepoints, not all used the same mid-year estimate. The clinical setting of AKI episodes were defined using the method developed by the author in project one. Inpatients triggering alerts following an in hospital measurement of SCr in the previous seven days were therefore classified as HA-AKI. Inpatients without a measurement of SCr in this timeframe were unable to be confidently classified as either HA- or CA-AKI and were excluded from all analyses. All other episodes were classified as CA-AKI.

**Outcome of AKI:** While not every study reported on all of the following, outcome of AKI was measured in a number of ways. This included 30- and 90-day mortality, recovery from AKI (defined by a SCr result within 30 days no longer in keeping with the definition of AKI), requirement of treatment in intensive care (defined by a measurement of SCr in an intensive care

setting within 7 days), peak AKI stage (defined by comparing the maximum SCr reached during a patient's episode with the baseline SCr associated with the alert), progression of AKI (defined by a peak AKI stage greater than the AKI stage associated with the alert, and for stage 3 alerts, more than a 50% rise in SCr from the alerting SCr), development of de novo CKD (defined by development of an eGFR <60 ml/min per 1.73 $m^2$ within 90 days) and for patients with pre-existing CKD, progression of pre-existing CKD (calculated using the latest eGFR value within 90 days of the alert and defined by a decline from baseline eGFR of more than 15% or 5 ml/min per 1.73 $m^2$). Some of the more longitudinal studies also included longer term survival analyses.

**Factors associated with incidence and outcome of AKI:** Since the seven local health boards in NHSW are each responsible for planning and delivering healthcare services for patients resident within their geographical area, the local health board area (as indicated by the 'NHSW organisation' field described in project one) was used to identify regional variation of AKI incidence across Wales. Other variables analysed by studies which addressed the second objective of this project included age, pre-existing CKD (defined by an eGFR <60 ml/min per 1.73 $m^2$ and calculated using baseline SCr and the CKD Epidemiology Collaboration eGFR equation), severity of AKI (defined using the stage of the AKI alert), socioeconomic status (defined using the Welsh Index for Multiple Deprivation score described in project one), admission to hospital (defined by a measurement of renal function in an inpatient setting within 7 days), clinical specialty associated with the AKI, interaction with healthcare services prior to the AKI (defined using measurements of renal function in the 30 day period prior to an AKI alert), follow-up care following AKI (defined by a repeat measurement of renal function within 7 or 30 days of an AKI alert), time of year and day of the week on which AKI is detected, and repeated episodes of AKI.

## 3.4 Published works by the author related to the epidemiology of AKI

This section presents 11 peer-reviewed publications by the author which together address the two objectives of this project. For each publication, the abstract followed by an evaluation of the work in the context of the overall thesis is provided. Because the abstracts refer to standalone papers all addressing a similar theme, there may be some unavoidable repetition.

### 3.4.1 Published work 1 (of 14 presented as part of this thesis)

| | |
|---|---|
| **Title:** | **Acute Kidney Injury in the era of the AKI e-alert** |
| **Reference:** | **Holmes J**, Rainer T, Geen J, Roberts G, May K, Wilson N, Williams JD, Phillips AO. Clinical Journal of the American Society of Nephrology. December 2016. |
| **Appendix:** | 3.1 |
| **Abstract:** | **Background/aim:** Our aim was to use a national electronic AKI alert to define the incidence and outcome of all episodes of community- and hospital-acquired adult AKI.<br>**Methods:** A prospective national cohort study was undertaken in a population of 3.06 million. Data were collected between March of 2015 and August of 2015. All patients with adult (≥18 years of age) AKI were identified to define the incidence and outcome of all episodes of community- and hospital-acquired AKI in adults. Mortality and renal outcomes were assessed at 90 days.<br>**Results:** There was a total of 31,601 alerts representing 17,689 incident episodes, giving an incidence of AKI of 577 per 100,000 population. Community-acquired AKI accounted for 49.3% of all incident episodes, and 42% occurred in the context of pre-existing CKD; 90-day mortality rate was 25.6%, and 23.7% of episodes progressed to a higher AKI stage than the stage associated with the alert. AKI electronic alert stage and peak AKI stage were associated with mortality, and mortality was significantly higher for hospital-acquired AKI compared with alerts generated in a community setting. Among patients who survived to 90 days after the AKI electronic alert, those who were not hospitalized had a lower rate of renal recovery and a greater likelihood of developing an eGFR<60 ml/min per 1.73 $m^2$ for the first time, which may be indicative of development of de novo CKD.<br>**Conclusions:** The reported incidence of AKI is far greater than the previously reported incidence in studies reliant on clinical identification of adult AKI or hospital coding data. Although an electronic alert system is Information Technology driven and therefore, lacks intelligence and clinical context, these data can be used to identify deficiencies in care, guide the development of appropriate intervention strategies, and provide a baseline against which the effectiveness of these interventions may be measured. |

**Evaluation of published work 1 in relation to thesis**

By using the data set developed in project one of this thesis, this first publication by the author sought to define and describe the incidence and outcome of HA- and CA-AKI in the adult population of Wales. The study found the overall incidence of AKI to be 577 per 100,000 population, far higher than rates reported by previous studies using clinical identification of AKI or hospital coding data. Consistent with previous smaller studies however, it found CA-AKI to

account for a significant proportion of AKI (49.3%). The study also observed a 30.1% 90-day mortality rate in HA-AKI and 22.3% in CA-AKI, which combined gave a significantly high 25.6% 90-day mortality rate following all AKI (Figure 3.1a). In the surviving cohort, for HA and CA combined, the study also found that almost a quarter of patients saw their AKI progress, more than 10% did not recover from their AKI, and more than a quarter either developed de novo CKD, or experienced progression of pre-existing CKD (Figure 3.1b). These results are presented in Table 3.1, which summarises the key findings of the five studies presented in this project which defined and described the incidence and outcome of AKI in different patient populations and/or healthcare settings.

This first publication also identified that there is significant regional variation in the incidence of AKI in the adult Welsh population, with incidence highest in areas served by Cwm Taf University Health Board (814 per 100,000 population) and lowest in areas served by Powys Teach Health Board (60 per 100,000 population). While the very low incidence observed in Powys likely reflects most of its population accessing care across the border and the rural nature of the area, it could also relate to the limited availability of healthcare services compared to other areas in Wales. The high incidence observed in Cwm Taf meanwhile likely reflects that this health board serves some of the most socially deprived populations of Wales (73 of the 188 (39%) LSOAs it serves are among the most deprived 20% of the 1909 LSOAs in Wales). Studies presented later (Published works 6 and 7) build on this finding further and explore exclusively the association of socioeconomic status with the incidence and outcome of AKI.

In addition to regional variation, this first study also explored the association of a number of other factors with the incidence and outcome of HA- and CA-AKI in the adult Welsh population. The results of these analyses and how they could be used to guide the development of appropriate intervention strategies are in Table 3.2.

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to better understand the epidemiology of AKI in the general adult Welsh population, including that which is acquired in the hospital and community setting. It has also identified that incidence and outcome of AKI varies in association with a number of factors, including local health board area, pre-existing CKD, severity of AKI, hospitalisation following AKI, and the clinical specialty associated with the AKI. Not only do the described findings provide a robust baseline from which interventions to improve the prevention and/or management of HA- and CA-AKI could be measured, they could also guide the development of these interventions. For instance, the data presented here would suggest such interventions may have greatest impact if targeted at stage 2 and 3 AKI in certain clinical areas and/or patients with pre-existing CKD and/or increasing hospital admission rates for those patients presenting with CA-AKI.

**Table 3.1:** Key findings of published works by the author which defined and described the incidence and outcome of AKI in different patient populations and/or healthcare settings

| **Published work** | **Patient population/ healthcare setting studied** | **Incidence of AKI** | **Outcome of AKI** |
|---|---|---|---|
| 1 | AKI in the adult Welsh population | 577 per 100,000 of the adult Welsh population, or 0.58% | 25.6% 90-day mortality rate, 23.7% AKI progression rate, 12.0% AKI non-recovery rate |
| | HA-AKI in the adult Welsh population | 50.7% of all AKI | 30.1% 90-day mortality rate |
| | CA-AKI in the adult Welsh population | 49.3% of all AKI | 22.3% 90-day mortality rate |
| 2 | AKI in the adult Welsh population identified in the primary care setting | 28.8% of all CA-AKI | 15.4% 90-day mortality rate, 40.5% pre-existing CKD progression rate, 18.1% AKI non-recovery rate |
| 3 | AKI in the adult Welsh population requiring treatment in the intensive care setting | 10.0% of all AKI | 38.2% 90-day mortality rate, 38.5% AKI progression rate, 19.1% AKI non-recovery rate |
| 4 | AKI in the paediatric Welsh population | 77.3 per 100,000 person-years, or 0.08% | 1.7% 30-day mortality rate, 94.0% AKI recovery rate |
| 5 | AKI in the adult Welsh renal transplant population | 35.4% of all renal transplant recipients | 19.8% 30-day mortality rate |

**Table 3.2:** Key findings of Published work 1

| **Variable** | **Association with incidence and/or outcome of AKI in the adult Welsh population** |
|---|---|
| Severity of AKI | The majority (78.7%) of AKI incidence is associated with the least severe stage of AKI, and more severe AKI is significantly associated with increased likelihood of death (AKI stage 2/3 vs. AKI stage 1; HR, 1.43; 95% CI, 1.34 to 1.54) and less recovery of renal function (AKI stage 2/3 vs. AKI stage 1; HR, 1.82; 95% CI, 1.64 to 2.03). From this finding, it could be concluded that interventions to improve the prevention and/or management of AKI in the adult Welsh population may therefore have greatest impact if targeted at stage 2 and 3 AKI. |
| Pre-existing CKD | A high proportion of AKI incidence is associated with pre-existing CKD (42.0%). From this finding, it could be concluded that interventions to improve the prevention and/or management of AKI in the adult Welsh population may therefore have greatest impact if targeted at patients with pre-existing CKD. |
| Clinical specialty associated with the AKI | Whereas the majority (25.0%) of HA-AKI is acquired in a general medical inpatient setting, followed by the combination of general surgery and trauma and orthopaedics (24.0%), the majority (53.0%) of CA-AKI that is not detected in primary care is detected in an accident and emergency setting (Figure 3.2). From this finding, it could be concluded that interventions to improve the prevention and/or management of AKI in the adult Welsh population may therefore have greatest impact if targeted at these clinical areas. |
| Hospitalisation following AKI | 82.0% of CA-AKI is admitted to hospital within seven days. These hospitalisations are most common in those patients presenting with more severe AKI, who are older and have pre-existing CKD (Figure 3.2), and are significantly associated with increased recovery from AKI (90.0% vs. 82.0%), less likelihood of developing de novo CKD (19.0% vs. 25.0%), but greater likelihood of death (HR, 1.31; 95% CI, 1.23 to 1.39). From this finding, it could be concluded that interventions to improve the management of CA-AKI in the adult Welsh population may therefore have greatest impact if targeted at increasing hospital admission rates for patients triggering AKI alerts in the community. |

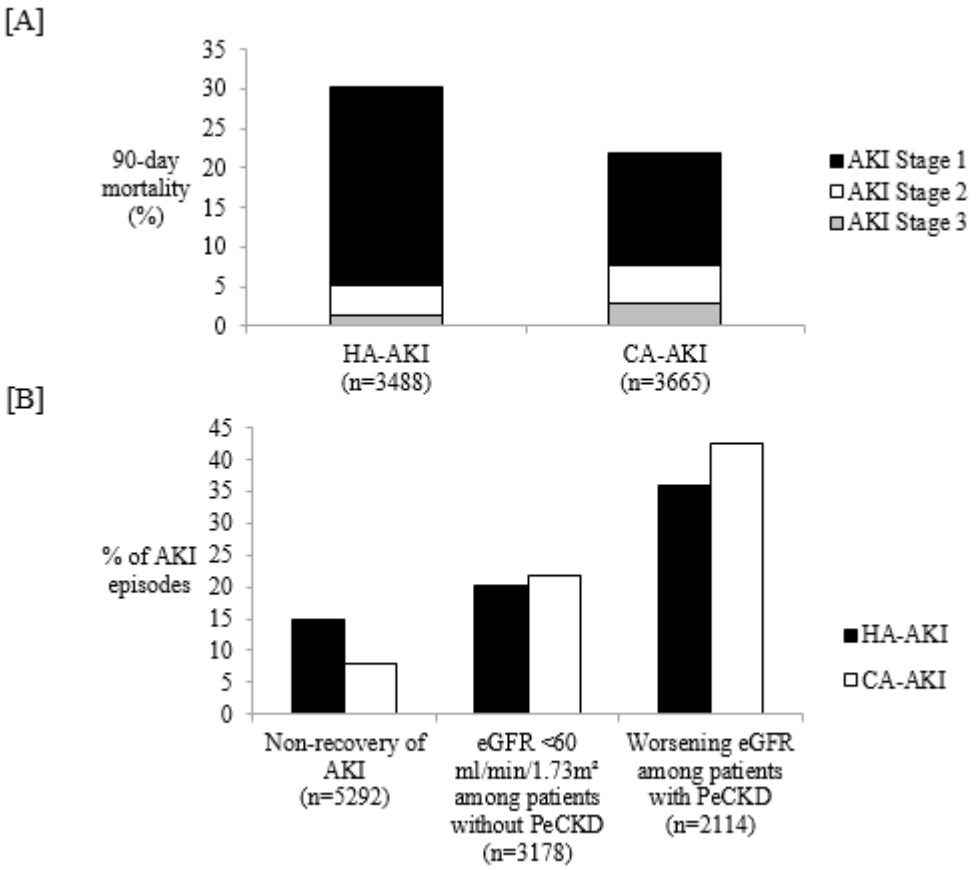



**Figure 3.1:** Outcomes of HA- and CA-AKI in the adult Welsh population: [A] 90-day mortality [B] Non-recovery from AKI, development of de novo CKD, and progression of pre-existing CKD

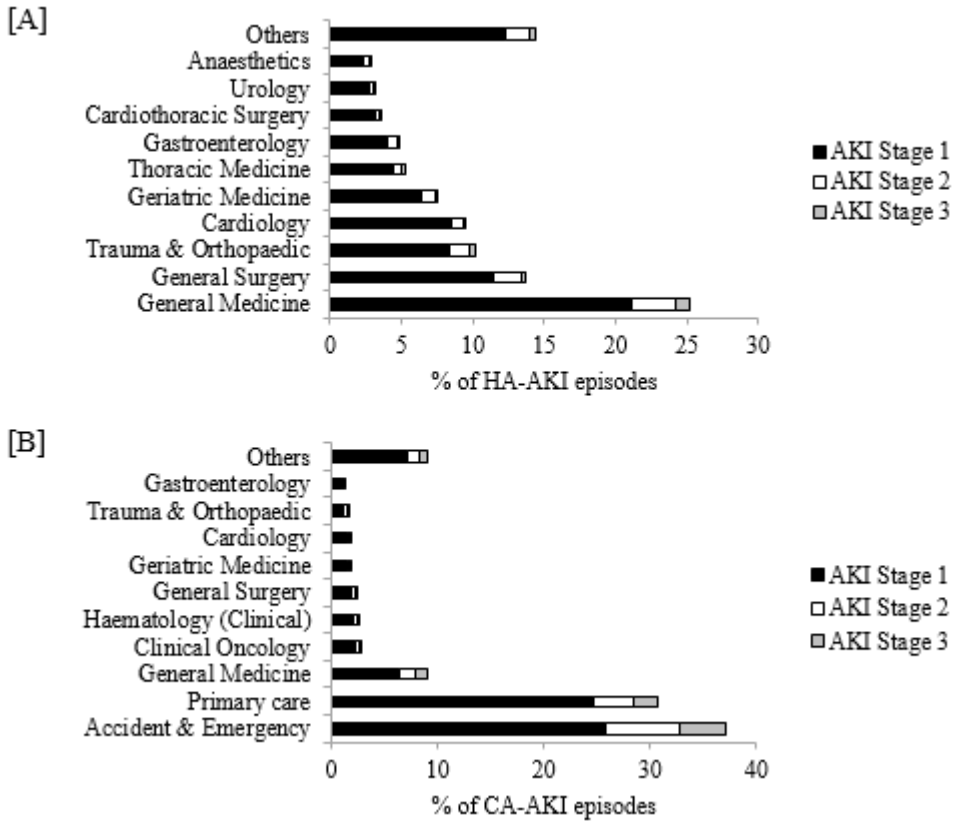



**Figure 3.2:** Clinical specialty associated with AKI in the adult Welsh population: [A] HA-AKI. [B] CA-AKI

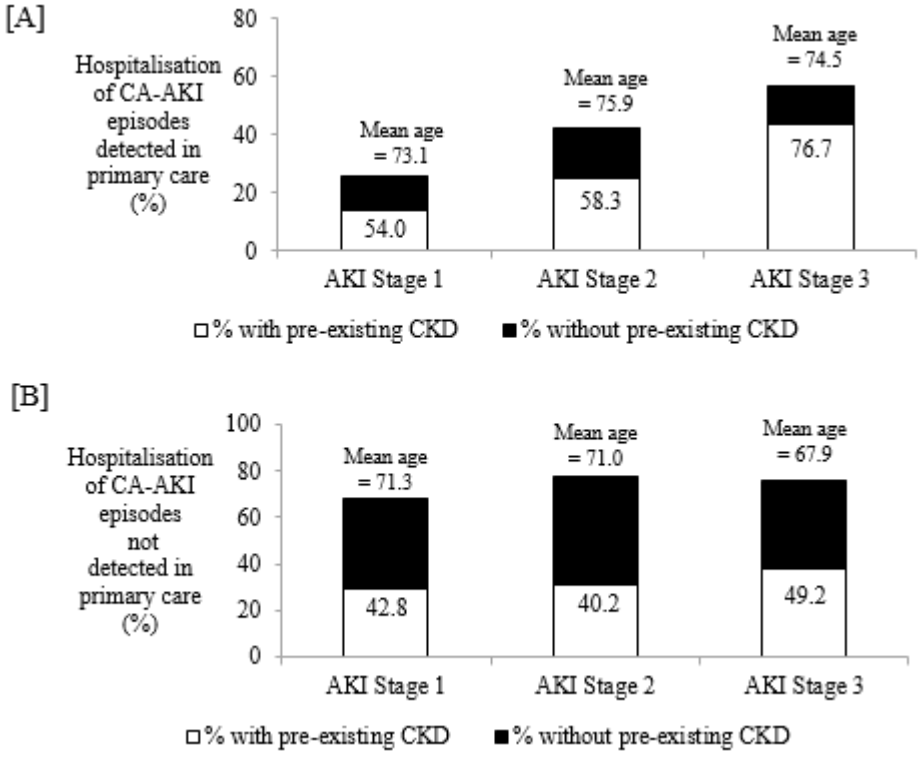



**Figure 3.3:** Hospitalisation following CA-AKI and its association with AKI severity, age and pre-existing CKD: CA-AKI detected in primary care [A] and not detected in primary care [B]

### 3.4.2 Published work 2

| | |
|---|---|
| **Title:** | **Acute kidney injury electronic alerts in primary care - findings from a large population cohort** |
| **Reference:** | **Holmes J,** Allen N, Roberts G, Geen J, Williams JD, Phillips AO. QJM: An International Journal of Medicine. September 2017. |
| **Appendix:** | 3.2 |
| **Abstract:** | **Background/aim:** Electronic reporting of AKI has been used to aid early AKI recognition although its relevance to CA-AKI and primary care has not been described. We described the characteristics and clinical outcomes of patients with CA-AKI, and AKI identified in primary care (PC-AKI) through AKI e-Alerts.<br>**Methods:** A prospective national cohort study was undertaken to collect data on all e-alerts representing adult CA-AKI. The study utilized the biochemistry based AKI electronic (e)-alert system that is established across the Welsh National Health Service.<br>**Results:** 28.8% of the 22 723 CA-AKI e-alerts were classified as PC-AKI. Ninety-day mortality was 24.0% and lower for PC-AKI vs. non-primary care (non-PC) CA-AKI. Hospitalization was 22.3% for PC-AKI and associated with greater disease severity, higher mortality, but better renal outcomes (non-recovery: 18.1% vs. 21.6%; progression of pre-existing CKD: 40.5% vs. 58.3%). 49.1% of PC-AKI had a repeat test within 7 days, 42.5% between 7 and 90 days, and 8.4% was not repeated within 90 days. There was significantly more non-recovery (24.0% vs. 17.9%) and progression of pre-existing CKD (63.3% vs. 47.0%) in patients with late repeated measurement of renal function compared to those with early repeated measurement of renal function.<br>**Conclusions:** The data demonstrate the clinical utility of AKI e-alerts in primary care. We recommend that a clinical review, or referral together with a repeat measurement of renal function within 7 days should be considered an appropriate response to AKI e-alerts in primary care. |

**Evaluation of published work 2 in relation to thesis**

By using the data set developed in project one of this thesis, this second publication by the author sought to define and describe the incidence and outcome of AKI in the adult Welsh population that is identified in primary care. Following Published work 1 and Figure 3.3, which suggested AKI detected in primary care differs from all other CA-AKI, this second study found that almost a third of all CA-AKI in the adult Welsh population is identified in primary care, around a fifth (22.3%) of these patients are admitted to hospital, 15.4% die within 90 days, and of those who survive, less than 90% recover from their AKI. While mortality was lower and progression of AKI was no different compared to AKI identified elsewhere in the community, patients with primary care identified AKI experienced significantly worse renal outcomes including, for those with pre-existing CKD, significantly more progression of CKD (58.3% vs. 40.5%, $P<0.001$) (Table 3.1). The study also found less than half (49.1%) of patients with primary care identified AKI received a repeat measurement of renal function within seven days, and that significantly worse renal outcome was associated with this cohort, with more non-recovery (24.0% vs. 17.9%) and progression of pre-existing CKD (63.3% vs. 47.0%).

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to better understand the epidemiology of AKI that is identified in the primary care setting. Not only do the described findings provide a robust baseline from which interventions to improve the management of AKI in this clinical setting could be measured, they could also guide the development of these interventions. Moreover, given what constitutes an appropriate response to AKI alerts in primary care is lacking, and detailed guidelines for the management of AKI in the community do not exist, this study's findings could help inform their development. The data presented here suggests a response which includes ensuring a clinical review and/or referral and/or repeat measurement of renal function within seven days may well offer improved outcomes for some patients following an AKI diagnosis in primary care.

### 3.4.3 Published work 3

| | |
|---|---|
| **Title:** | **Utility of electronic AKI alerts in intensive care: A national multicentre cohort study** |
| **Reference:** | **Holmes J,** Roberts G, Geen J, Dodd A, Selby NM, Lewington A, Scholey G, Williams JD, Phillips AO. Journal of Critical Care. April 2018. |
| **Appendix:** | 3.3 |
| **Abstract:** | **Background/aim:** 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.<br>**Methods:** A prospective cohort study was undertaken between November 2013 and April 2016, collecting data on electronic AKI alerts issued.<br>**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, recovery of renal function was significantly higher following HA-AKI (84.2%, $p=0.004$) and CA-AKI (87.6%, $p<0.001$) compared to patients alerting on the ICU (78.3%).<br>**Conclusions:** The study provides a nationwide characterisation of AKI in ICU highlighting the high incidence and its impact on patient outcome. The data also suggests that within the cohort of AKI patients treated in the ICU there are significant differences in the presentation and outcome between those patients that require transfer to the ICU after AKI is identified and those who develop AKI following ICU admission. Moreover, the study demonstrates that 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. |

**Evaluation of published work 3 in relation to thesis**

By using the data set developed in project one of this thesis, this third publication by the author sought to define and describe the incidence and outcome of AKI in the adult Welsh population that requires treatment in the intensive care setting. The study found that 10% of all AKI in the adult Welsh population is associated with treatment in intensive care, 48.8% of which is AKI identified in ICU and 51.2% is AKI transferred to ICU. While in the surviving cohort, 38.5% of patients saw their AKI progress and almost a fifth did not recover from their AKI (Table 3.1), the study also observed a significantly high 38.2% 90-day mortality rate following all AKI requiring treatment in ICU, and better overall survival for patients with AKI identified in ICU compared to those with AKI transferred to ICU (Figure 3.4).

To put this published work in to context of the overall thesis, it has used data on AKI alerts to better understand the epidemiology of AKI that is treated in the intensive care setting. Not only do the described findings provide a robust baseline from which interventions to improve the

management of AKI in this clinical setting could be measured, they could also guide the development of these interventions. The data presented here suggests that this could include the earlier transfer of patients by critical care outreach teams to the ICU following an AKI diagnosis, which may in some cases, offer improved outcomes.

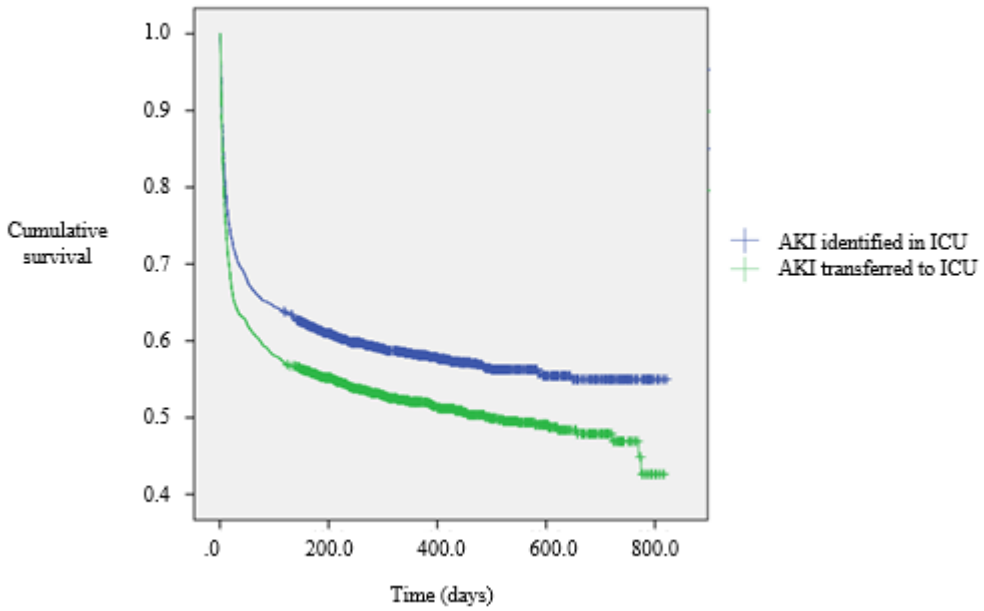



**Figure 3.4:** Kaplan-Meier survival curves for AKI requiring treatment in intensive care

### 3.4.4 Published work 4

| | |
|---|---|
| **Title:** | **Acute Kidney Injury in Children Based on Electronic Alerts** |
| **Reference:** | Gubb S, **Holmes J**, Smith G, Geen J, Williams JD, Phillips AO. Journal of Pediatrics. November 2019. |
| **Appendix:** | 3.4 |
| **Abstract:** | **Aim:** To define the incidence and outcome of acute kidney injury (AKI) in paediatrics using data collected from a national electronic alert system.<br>**Methods:** 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.<br>**Results:** There were 2472 alerts in a total of 1719 patients, giving an incidence of 77.3 per 100,000 person-years. Of the patients, 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. Thirty-day mortality was 1.7% but was significantly higher in hospital-acquired AKI (2.1%), compared with community-acquired 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 community-acquired AKI (69.7%) compared with hospital-acquired 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 1 AKI episode. Repeated episodes of AKI were associated with increased 30-mortality (11.6% vs 4.6%, $P < 0.001$) and higher residual renal impairment (13.3% vs 5.4%, $P < 0.001$).<br>**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 (SCr), triggered by a SCr level that may be interpreted as being normal despite a significant increase from the baseline for the patient. |

**Evaluation of published work 4 in relation to thesis**

By using the data set developed in project one of this thesis, this fourth publication by the author sought to define and describe the incidence and outcome of AKI in the paediatric population of Wales. The study found the overall incidence of AKI to be 77.3 per 100,000 of the Welsh paediatric population, far higher than rates reported by previous studies using clinical identification of AKI or hospital coding data. Consistent with Published work 1 and AKI in adults, it found a significant proportion of AKI in children is also acquired outside of the hospital setting (30.5%). It observed significantly better outcomes compared to AKI seen in adults however, including a 2.1% 30-day mortality rate in HA-AKI and 0.8% in CA-AKI, which combined gave a 1.7% 30-day mortality rate following all paediatric AKI. The study also found that a significant proportion of patients (39.6%) did not receive a repeat measurement of renal function within 30 days following an alert and repeated episodes of AKI were associated with significantly worse outcomes, including higher 30-day mortality rates (11.6% vs 4.6%, $P < 0.001$) and lower rates of recovery (5.4% vs 13.3%, $P < 0.001$).

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to better understand the epidemiology of AKI in children, including that which is acquired in the hospital and community setting. Moreover, not only do the described findings provide a robust baseline from which interventions to improve the prevention and management of paediatric AKI could be measured, they could also guide the development of these interventions. The data presented here suggest that this could include more frequent monitoring of renal function in children following AKI, which could in some cases, improve outcomes for paediatric patients who develop AKI.

### 3.4.5 Published work 5

| | |
|---|---|
| **Title:** | **Using electronic AKI alerts to define the epidemiology of acute kidney injury in renal transplants** |
| **Reference:** | Jones A, **Holmes J**, Stephens M, Geen J, Williams JD, Donovan K, Phillips AO. Journal of Nephrology. December 2020. |
| **Appendix:** | 3.5 |
| **Abstract:** | **Background/aim:** Little is known regarding the impact of AKI on renal transplant outcome. Our aim was to define the incidence and outcome of AKI in renal transplant patients using data collected from a national AKI alert system<br>**Methods:** The study represents a prospective national cohort study collecting data on 1224 renal transplants recipients with a functioning renal transplant, between April 2015 and March 2019.<br>**Results:** 444 patients experienced at least one episode of AKI giving an incidence rate of 35.4%. 64.7% of episodes were AKI stage 1, 7.3% AKI stage 2 and 28% AKI stage 3. Only 6.2% of episodes occurred in the context of rejection. 43.5% of AKI episodes were associated with sepsis. AKI was associated with pre-existing renal dysfunction, and a primary renal diagnosis of diabetic nephropathy. AKI was more prevalent in recipients from a donor after cardiac death (26.4% vs. 21.4%, $p < 0.05$) compared to the non-AKI cohort. Following AKI, 30-day mortality was 19.8% and overall mortality was 34.8%, compared to 8.4% in the non AKI cohort (RR 4.06, 95% CI 3.1–5.3, $p < 0.001$). Graft survival (GS), and death censored graft survival (DCGS) censored at 4 years, in the AKI cohort were significantly lower than in the non AKI group ($p < 0.0001$ for GS and DCGS).<br>**Conclusions:** The study provides a detailed characterisation of AKI in renal transplant recipients highlighting its significant negative impact on patient and graft survival. |

**Evaluation of published work 5 in relation to thesis**

By using the data set developed in project one of this thesis, this fifth publication by the author sought to define and describe the incidence and outcome of AKI in the adult renal transplant population of Wales. The study found AKI to occur in over a third (35.4%) of patients living with a renal transplant, and that one in five of these are likely to die within 30 days and only a quarter are likely to recover from their AKI (Table 3.1). It also found transplant patients developing AKI experience significantly worse outcomes compared to those transplant patients who do not experience AKI, including higher rates of 30-day mortality and lower rates of graft survival.

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to better understand the epidemiology of AKI in the renal transplant population. Moreover, while further and more longitudinal studies may be required, not only do the described findings provide a robust baseline from which interventions to improve the prevention and management of AKI in this patient cohort could be measured, they could also guide the development of these interventions. The data presented here suggest this could include more frequent monitoring of renal function in transplant recipients post-transplant, to minimise the development of AKI, and therefore improve outcomes.

### 3.4.6 Published works 6 and 7

| | |
|---|---|
| **Title:** | **The influence of socioeconomic status on presentation and outcome of acute kidney injury** |
| **Reference:** | Phillips D, **Holmes J**, Davies R, Geen J, Williams JD, Phillips AO. QJM: An International Journal of Medicine. December 2018. |
| **Appendix:** | 3.6 |
| **Abstract:** | **Background/aim:** Although socioeconomic background is known to impact on the incidence and progression of chronic kidney disease, its influence on the presentation and outcome for acute kidney injury is not known and is the subject of this study.<br>**Methods:** The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients >18 years of age between March 2015 and November 2017. Socioeconomic classification of patients was derived from the Welsh Index Multiple Deprivation score (WIMD). Patients were grouped according to the WIMD score by their postcode, and the ranked data were categorized into percentiles and correlated with incidence and measures of AKI severity and outcome.<br>**Results:** Data was collected on a total of 57,654 patients. Increased deprivation was associated with higher AKI incidence rates, more episodes of AKI per patient and more severe AKI at presentation. In contrast 90-day mortality was highest in the most affluent areas. Mortality in affluent areas was driven by increased patient age. Corrected for age 90-day mortality was higher in areas of increased deprivation.<br>**Conclusions:** This study highlights that AKI incidence presentation and outcomes are adversely affected by social deprivation. Further studies are required to understand the extent to which these differences reflect patient related factors or regional differences in provision and access to care. |

| | |
|---|---|
| **Title:** | **Acute Kidney Injury, Age, and Socioeconomic Deprivation: Evaluation of a National Data Set** |
| **Reference:** | **Holmes J**, Phillips D, Donovan K, Geen J, Williams JD, Phillips AO. Kidney International Reports. March 2019. |
| **Appendix:** | 3.7 |
| **Abstract:** | **Background/aim:** This study examined the relationship among age, measures of social deprivation, and incidence and outcome of acute kidney injury (AKI).<br>**Methods:** The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients 18 years or older between March 2015 and January 2017. Patients were grouped according to their WIMD score, and Multivariate Cox proportional hazard modelling was used to adjust the data for age. The ranked data were categorized into percentiles and correlated with incidence, and measures of AKI severity and outcome.<br>**Results:** Analysis included 57,654 patients. For the whole cohort, the highest 90-day survival was associated with the most socially deprived cohorts. There was a significant negative relationship between age-adjusted incidence of AKI and the WIMD score. In patients 60 years or older, there was an inverse correlation between WIMD score and survival that was not evident in those younger than 60. AKI severity at presentation was worse in patients from areas of social deprivation. Social deprivation was associated with a significantly higher proportion of pre-existing chronic kidney disease (CKD) in patients with AKI older than 60, but not in those younger than 60.<br>**Conclusions:** Overall mortality following AKI was higher in least-deprived areas, reflecting an older patient cohort. In contrast, social deprivation was associated with higher age-adjusted AKI incidence and age-adjusted mortality following AKI. The excess mortality observed in more deprived areas was associated with more severe AKI and a higher proportion of pre-existing CKD. |

**Evaluation of published works 6 and 7 in relation to thesis**

By using the data set developed in project one of this thesis, these sixth and seventh publications by the author explored the association of social deprivation, age and pre-existing CKD with variation in the incidence and outcome of AKI in the adult population of Wales. While the two separate studies found increased social deprivation associated with increased incidence of AKI, both studies found increased social deprivation associated with better outcome following AKI. Whereas Published work 6 found AKI incidence rates to be highest in the most socially deprived areas (Figure 3.5a), in contrast, it found 90-day AKI associated mortality rates to be highest in the least socially deprived areas (Figure 3.5b), reflecting an older patient cohort (Figure 3.5c) and higher proportion of patients with pre-existing CKD (Figure 3.5d) living in less socially deprived areas. Once corrected for the described factors however, rates of 90-day AKI associated mortality were higher in areas of increased deprivation.

Published work 7 also found a significant association between increased social deprivation and both age-adjusted incidence of AKI and age-adjusted mortality following AKI. It also found the positive correlation seen in Published work 6, between increased social deprivation and increased unadjusted 90-day survival following AKI, to be significant only in patients aged 60 years or older (Figure 3.6), for both HA- and CA-AKI. From this finding, it could be concluded that in addition to age, lifestyle and comorbidity, socioeconomic factors like the availability and accessibility of healthcare services may also affect the incidence and outcome of AKI. The finding described therefore also highlights that improving the incidence and outcome of AKI likely requires influencing complex and long term inequalities which in turn likely requires social, economic and medical interventions at the population level. For instance, the findings described suggest that interventions aimed at improving the prevention and/or management of AKI in the adult Welsh population may have greatest impact if targeted at areas of increased social deprivation, and at patients who live in these socially deprived areas who are aged less than 60 years and/or who have pre-existing CKD.

To put these two published works in to context of the overall thesis, they have used national data on AKI alerts to identify that the incidence and outcome of AKI in the adult Welsh population varies in association with social deprivation, age and pre-existing CKD. Not only do the described findings help to better understand the epidemiology of AKI, they could also guide the development of interventions to improve the prevention and management of AKI. Further studies are nonetheless required to further understand the extent to which the impact of socioeconomic status on the presentation and outcome of AKI observed in the studies here reflect patient related factors or differences in healthcare provision and/or access.

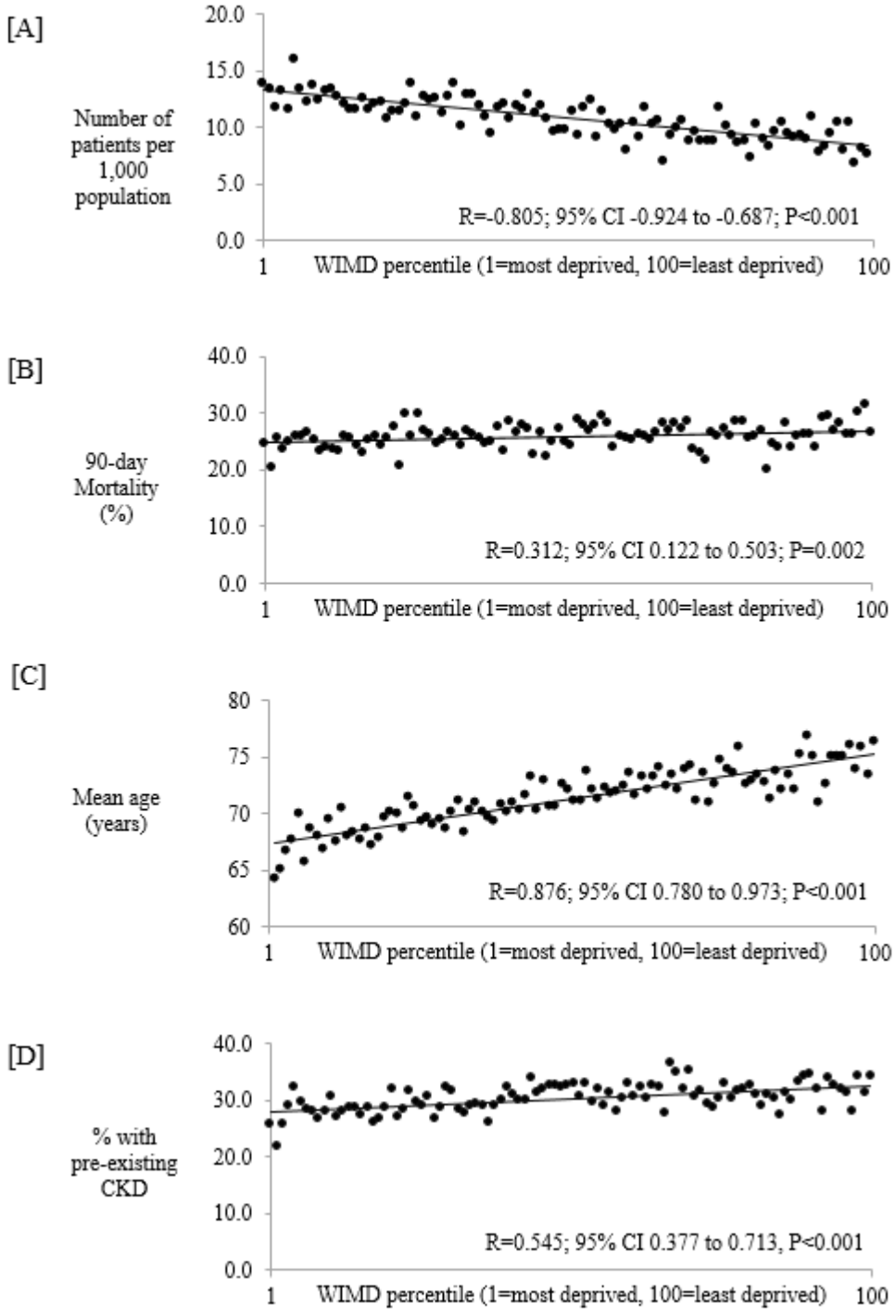
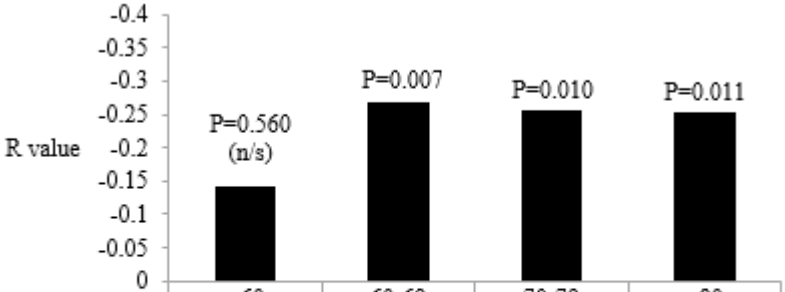



**Figure 3.5:** Association of socioeconomic status, age and pre-existing CKD with the incidence and outcome of AKI: [A] Correlation of socioeconomic status and incidence of AKI [B] Correlation of socioeconomic status and 90-day AKI associated mortality [C] Correlation of socioeconomic status and age [D] Correlation of socioeconomic status and pre-existing CKD




| | <60 | 60-69 | 70-79 | ≥80 |
|---|---|---|---|---|
| R | -0.142 | -0.267 | -0.256 | -0.253 |
| Lower 95% CI | -0.258 | -0.460 | -0.450 | -0.447 |
| Upper 95% CI | -0.058 | -0.073 | -0.063 | -0.059 |

**Figure 3.6:** Correlation between social deprivation and 90-day AKI associated mortality for different age groups

### 3.4.7 Published work 8

| | |
|---|---|
| **Title:** | **Community acquired acute kidney injury: findings from a large population cohort** |
| **Reference:** | **Holmes J**, Geen J, Phillips B, Williams JD, Phillips AO. QJM: An International Journal of Medicine. November 2017. |
| **Appendix:** | 3.8 |
| **Abstract:** | **Background/aim:** The extent of patient contact with medical services prior to development of community acquired-acute kidney injury (CA-AKI) is unknown. We examined the relationship between incident CA-AKI alerts, previous contact with hospital or primary care and clinical outcomes.<br>**Methods:** A prospective national cohort study of all electronic AKI alerts representing adult CA-AKI. Data were collected for all cases of adult (≥18 years of age) CA-AKI in Wales between 1 November 2013 and 31 January 2017.<br>**Results:** There were a total of 50 560 incident CA-AKI alerts. In 46.8% there was a measurement of renal function in the 30 days prior to the AKI alert. In this group, in 63.8% this was in a hospital setting, of which 37.6% were as an inpatient and 37.5% in Accident and Emergency. Progression of AKI to a higher AKI stage (13.1 vs. 9.8%, $P < 0.001$) (or for AKI 3 an increase of > 50% from the creatinine value generating the alert), the proportion of patients admitted to Intensive Care (5.5 vs. 4.9%, $P = 0.001$) and 90-day mortality (27.2 vs. 18.5%, $P < 0.001$) was significantly higher for patients with a recent test. 90-day mortality was highest for patients with a recent test taken in an inpatient setting prior to CA-AKI (30.9%).<br>**Conclusions:** Almost half of all patients presenting with CA-AKI are already known to medical services, the majority of which have had recent measurement of renal function in a hospital setting, suggesting that AKI for at least some of these may potentially be predictable and/or avoidable. |

**Evaluation of published work 8 in relation to thesis**

By using the data set developed in project one of this thesis, this eighth publication by the author explored the association of a previous interaction with healthcare services with variation in the incidence and outcome of CA-AKI in the adult Welsh population. The study found that almost half (46.8%) of all patients presenting with CA-AKI are already known to healthcare services, with almost two thirds (63.8%) of which having received a measurement of renal function in a hospital setting during the 30 day period prior to alerts. It also found a previous interaction with healthcare services to be associated with significantly worse outcomes, including more progression of AKI (13.1 vs. 9.8%), more requirement of treatment in intensive care (5.5 vs. 4.9%) and higher rates 90-day mortality (27.2 vs. 18.5%).

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to identify that a large proportion of CA-AKI may relate to a recent hospitalisation. Not only does this study help to better understand the epidemiology of CA-AKI, it also could guide the development of interventions to improve the prevention and management of CA-AKI. The data here would suggest that this could include earlier and more frequent monitoring of patients following discharge from hospital, to in some cases, predict and therefore prevent the

development of AKI. Moreover, given detailed guidelines for the management of AKI in the community are lacking, the findings described here could help their development.

### 3.4.8 Published work 9

| | |
|---|---|
| **Title:** | **Seasonal pattern of incidence and outcome of Acute Kidney Injury: A national study of Welsh AKI electronic alerts** |
| **Reference:** | Phillips D, Young O, **Holmes J**, Allen LA, Roberts G, Geen J, Williams JD, Phillips AO. International Journal of Clinical Practice. September 2017. |
| **Appendix:** | 3.9 |
| **Abstract:** | **Background/aim:** To identify any seasonal variation in the occurrence of, and outcome following AKI.<br>**Methods:** The study utilised the biochemistry based AKI electronic (e)-alert system established across the Welsh National Health Service to collect data on all AKI episodes to identify changes in incidence and outcome over one calendar year (1st October 2015 and the 30th September 2016).<br>**Results:** There were total of 48 457 incident AKI alerts. The highest proportion of AKI episodes was seen in the quarter of January to March (26.2%), and the lowest in the quarter of October to December (23.3%, $P < 0.001$). The same trend was seen for both community-acquired and hospital-acquired AKI sub-sets. Overall 90 day mortality for all AKI was 27.3%. In contrast with the seasonal trend in AKI occurrence, 90 day mortality after the incident AKI alert was significantly higher in the quarters of January to March and October to December compared with the quarters of April to June and July to September ($P < 0.001$) consistent with excess winter mortality reported for likely underlying diseases which precipitate AKI.<br>**Conclusions:** In summary we report for the first time in a large national cohort, a seasonal variation in the incidence and outcomes of AKI. The results demonstrate distinct trends in the incidence and outcome of AKI. |

**Evaluation of published work 9 in relation to thesis**

By using the data set developed in project one of this thesis, this ninth publication by the author explored whether there is seasonal variation in the incidence and outcome of AKI in the adult population of Wales. The study found significant seasonal variation in the incidence of AKI with the highest incidence observed in the quarter of January to March (26.2%), and the lowest observed in the quarter of October to December (23.3%), with this trend consistent across both HA- and CA-AKI (Figure 3.7). It also found outcome of AKI to vary significantly depending on the time of year in which the AKI was detected, but in contrast to AKI incidence, rates of 90-day AKI associated mortality were highest in the quarters of January to March (29.4%) and October to December (28.1%). These differences likely reflect well-documented excess winter mortality associated with numerous primary underlying illnesses which precipitate AKI.

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to identify that there is seasonal variation in the incidence and outcome of AKI in the adult population of Wales. While further studies involving data on clinical diagnosis and cause of death are required to further understand these trends, the described findings nonetheless help to better understand the epidemiology of AKI and could guide the development of interventions to improve the prevention and management of AKI.

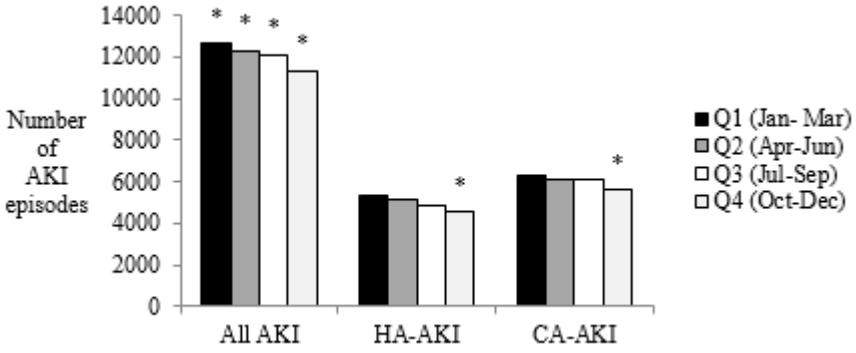



**Figure 3.7:** Seasonal variation in AKI incidence. * *p <0.001 vs. all other quarters*

### 3.4.9 Published work 10

| | |
|---|---|
| **Title:** | **Adding a new dimension to the weekend effect: an analysis of a national data set of electronic AKI alerts** |
| **Reference:** | **Holmes J**, Rainer T, Geen J, Williams JD, Phillips AO. QJM: An International Journal of Medicine. April 2018. |
| **Appendix:** | 3.10 |
| **Abstract:** | **Background/aim:** Increased mortality related to differences in delivery of weekend clinical care is the subject of much debate. We compared mortality following detection of acute kidney injury (AKI) on week and weekend days across community and hospital settings.<br>**Methods:** A prospective national cohort study, with AKI identified using the Welsh National electronic AKI reporting system. Data were collected on outcome for all cases of adult AKI in Wales between 1 November 2013 and 31 January 2017.<br>**Results:** There were a total of 107 298 episodes. Weekday detection of AKI was associated with 28.8% (26 439) 90-day mortality compared to 31.9% (4551) for AKI detected on weekdays (RR: 1.11, 95% CI: 1.08–1.14, $P < 0.001$, HR: 1.16 95% CI: 1.12–1.20, $P < 0.001$). There was no 'weekend effect' for mortality associated with hospital-acquired AKI. Weekday detection of community-acquired AKI (CA-AKI) was associated with a 22.6% (10 356) mortality compared with weekend detection of CA-AKI, which was associated with a 28.6% (1619) mortality (RR: 1.26, 95% CI: 1.21–1.32, $P < 0.001$, HR: 1.34, 95%CI: 1.28–1.42, $P < 0.001$). The excess mortality in weekend CA-AKI was driven by CA-AKI detected at the weekend that was not admitted to hospital compared with CA-AKI detected on weekdays which was admitted to hospital (34.5% vs. 19.1%, RR: 1.8, 95% CI: 1.69–1.91, $P < 0.001$, HR: 2.03, 95% CI: 1.88–2.19, $P < 0.001$).<br>**Conclusions:** 'Weekend effect' in AKI relates to access to in-patient care for patients presenting predominantly to hospital emergency departments with AKI at the weekend. |

**Evaluation of published work 10 in relation to thesis**

By using the data set developed in project one of this thesis, this tenth publication by the author explored whether the incidence and outcome of AKI in the adult Welsh population varies according to the day of the week on which the AKI is detected. The study found significantly more AKI is detected during the week than on the weekend, with average daily incidence rates, expressed by the proportion of the total weekly AKI incidence, 17.3% for Monday through Friday and 6.7% for Saturday and Sunday. It also found significantly worse 90-day mortality rates for AKI that is detected on the weekend compared to AKI that is detected during the week (31.9% vs. 28.8%). With no such difference observed in HA-AKI, this increased mortality at the weekend was driven entirely by CA-AKI (28.6% vs. 22.6%), which in turn was driven by non-admission to hospital, as demonstrated by a 34.5% mortality rate associated with CA-AKI detected on weekends which was not admitted to hospital, compared to 19.1% for CA-AKI detected on weekdays which was admitted to hospital. From these findings, it could be concluded that in AKI, the so-called 'weekend effect', which refers to differences in healthcare delivery at the weekend, relates mostly to changing patterns of admission for CA-AKI at the weekend. Possible

explanations for this could include inappropriate delay in hospital discharge at weekends, and reduced availability of primary care services and diagnostics at weekends.

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to identify that rather than inequity of hospital based care at the weekend, the 'weekend effect' in AKI predominantly relates to limited access to inpatient care at the weekend for patients presenting with AKI at hospital emergency departments. While further studies involving hospital episode statistics (HES), and data on resource allocation and/or healthcare staffing models may be required to further understand these trends, the described findings nonetheless add to the wider discussion that the adoption of a 7-day team-based model of healthcare, which increases discharges and access to primary care at weekends, could improve patient flow and reduce variation in care.

### 3.4.10 Published work 11

| | |
|---|---|
| **Title:** | **Recurrent acute kidney injury: predictors and impact in a large population-based cohort** |
| **Reference:** | **Holmes J**, Geen J, Williams JD, Phillips AO. Nephrology Dialysis Transplantation. July 2019. |
| **Appendix:** | 3.11 |
| **Abstract:** | **Background/aim:** This study examined the impact of recurrent episodes of acute kidney injury (AKI) on patient outcomes.<br>**Methods:** The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients ≥18 years of age between April 2015 and September 2018. Patients were grouped according to the number of AKI episodes they experienced with each patient's first episode described as their index episode. We compared the demography and patient outcomes of those patients with a single AKI episode with those patients with multiple AKI episodes. Analysis included 153 776 AKI episodes in 111 528 patients.<br>**Results:** Of those who experienced AKI and survived their index episode, 29.3% experienced a second episode, 9.9% a third episode and 4.0% experienced fourth or more episodes. Thirty-day mortality for those patients with multiple episodes of AKI was significantly higher than for those patients with a single episode (31.3% versus 24.9%, $P < 0.001$). Following a single episode, recovery to baseline renal function at 30 days was achieved in 83.6% of patients and was significantly higher than for patients who had repeated episodes (77.8%, $P < 0.001$). For surviving patients, non-recovery of renal function following any AKI episode was significantly associated with a higher probability of a further AKI episode (33.4% versus 41.0%, $P < 0.001$). Furthermore, with each episode of AKI the likelihood of a subsequent episode also increased (31.0% versus 43.2% versus 51.2% versus 51.7% following a first, second, third and fourth episode, $P < 0.001$ for all comparisons).<br>**Conclusions:** The results of this study provide an important contribution to the debate regarding the need for risk stratification for recurrent AKI. The data suggest that such a tool would be useful given the poor patient and renal outcomes associated with recurrent AKI episodes as highlighted by this study. |

**Evaluation of published work 11 in relation to thesis**

By using the data set developed in project one of this thesis, this eleventh and final publication to be included in this project explored whether variation in the outcome of AKI is associated with repeated episodes of AKI. The study found almost a third (29.3%) of patients who survive their index episode of AKI experience at least one additional episode. It also found 30-day AKI associated mortality and recovery from AKI to be significantly worse for patients with multiple episodes compared to those patients with a single episode (Figure 3.8), and that following any AKI episode there is significant association between non-recovery and the probability of a recurrent episode (Figure 3.9).

To put this published work in to context of the overall thesis, it has used national data on AKI alerts to identify that repeated episodes of AKI are common and likely lead to a worse prognosis. While further and more longitudinal studies may be required to further explore this conclusion,

the described findings nonetheless support previous studies in the literature which propose the development of tools for predicting patients at most risk of experiencing recurrent AKI.

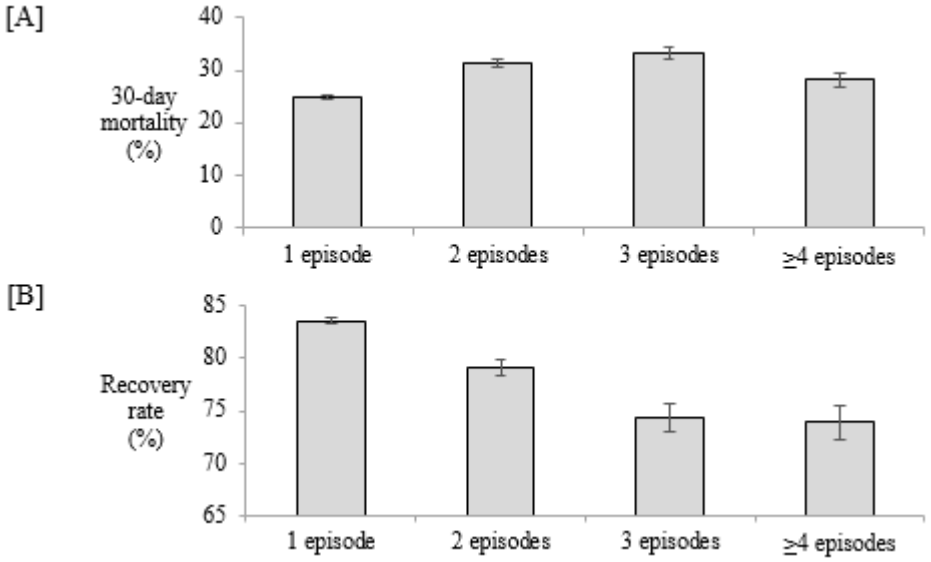



**Figure 3.8:** Outcomes associated with repeated episodes of AKI: [A] 30-day mortality [B] Recovery from AKI. *Error bars indicate 95% confidence intervals*

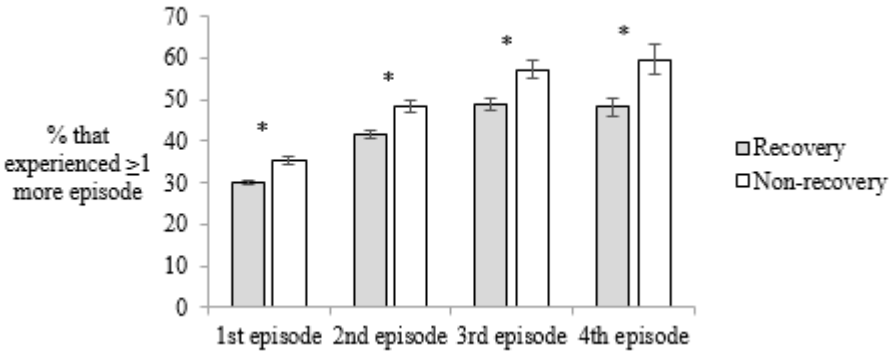



**Figure 3.9:** Relationship between recovery and repeated AKI episodes. *Error bars indicate 95% confidence intervals and * indicate significant differences (p <0.001) between recovery and non-recovery*

### 3.5 Summary of project

In addressing the second aim of the thesis, this second project has presented 11 peer-reviewed publications by the author which collectively provide a comprehensive epidemiological description of AKI. The studies presented have followed two themes. While some have utilised national data on AKI alerts and therefore routine SCr data, to define and describe the incidence and outcome of AKI in different patient populations and/or healthcare settings, others have explored and identified factors associated with variation in the incidence and/or outcome of AKI. This has included:

- Defining and describing the incidence and outcome of AKI in the:
    - adult,
    - paediatric, and
    - renal transplant populations of Wales, and in the
    - hospital,
    - community,
    - primary care, and
    - intensive care setting.

- Exploring the association of the following factors with the incidence and/or outcome of AKI:
    - age,
    - pre-existing CKD,
    - socioeconomic status,
    - local health board area,
    - severity of the AKI,
    - clinical specialty associated with the AKI,
    - hospitalisation following AKI,
    - interaction with healthcare services prior to AKI,
    - follow-up care following AKI,
    - seasonal variation,
    - the ‘weekend effect’, and
    - repeated episodes of AKI.

By applying the data set developed by the author in project one of this thesis, the studies presented in this project help better understand the epidemiology of AKI. Some of their conclusions could also meanwhile be used to guide the development of interventions to improve the prevention and/or management of AKI. Therefore, and in the context of the overall thesis, the work

documented here could be described as demonstration of these data's potential for epidemiological research in AKI, as well as QI in healthcare provision related to AKI. Moreover, because they utilised the aforementioned novel data set, the publications presented represent some of the first national, multicentre, and population-based studies to describe AKI and its associated factors. The author therefore proposes that they significantly add to the literature to which they relate.

# Chapter 4: Project 3

## Application of a national data set for QI in healthcare provision related to AKI

### 4.1 Introduction

While project two could primarily be described as documenting the potential of the data set developed by the author in project one for informing the epidemiology of AKI, this third and final project of the portfolio style thesis explores and documents practical examples of these data's potential for informing QI in healthcare provision related to AKI. Comprised of two parts, it first presents two peer-reviewed studies by the author which by applying the described data set, sought to investigate potential opportunities to refine the clinical utility of the AKI alerting system described in this thesis. These studies followed concern among some clinicians that such systems could generate large numbers of alerts which could lead to so-called 'alert fatigue', whereby alerts are missed and/or ignored by clinicians regardless of their importance. This was problematic and risked undermining the primary purpose of the system.

While the author's studies presented in project two may provide a baseline from which the impact of interventions aimed at improving the quality of healthcare provision related to AKI in Wales could be measured, it was also important for this quality to be measurable over time. As discussed in previous chapters, the QI literature states without measurement, improvement is not possible (Deming, 1986; Drucker, 1997). It is intuitive that without measurement, it is impossible to determine if, and to what extent, interventions improve quality as expected. The second part of this project describes the work undertaken by the author to develop a tool which could be used to robustly measure, monitor and compare the quality of healthcare provision related to AKI in Wales, a mechanism which did not exist prior. To demonstrate the potential of such a tool for QI, and endorse its potential widespread and routine adoption, the project concludes with a further and final peer-reviewed publication written by the author.

## 4.2 Aims and objectives

In addressing the third aim of the thesis, the aim of this project was to explore and demonstrate the potential of the national AKI data set developed by the author in project one, for QI in healthcare provision related to AKI. To achieve this aim, the objectives of the project were as follows:

1. Demonstrate the clinical significance of alerts transmitted by the Welsh AKI alerting system.
2. Investigate potential opportunities to refine the clinical utility of the Welsh AKI alerting system.
3. Develop a tool which could be used to inform QI in healthcare provision related to AKI in Wales.

## 4.3 Published works by the author related to the clinical utility of AKI alerts

This section presents two peer-reviewed publications by the author (Appendix 4.1 and 4.2) which together address objectives one and two of this project. For each publication, the rationale, abstract and an evaluation of the work in the context of the overall thesis is provided.

### 4.3.1 Published work 12 (of 14 presented as part of thesis)

**Rationale**

Consensus definitions of AKI are dependent on temporal changes in SCr, either within 48 hours or seven days. Not all patients developing AKI will have received a measurement of SCr within these timeframes however and Siew *et al.* (2010) previously report that definitions of AKI which discount preadmission measurements of SCr likely leads to under-diagnosis of AKI. In the absence of a recent SCr measurement, and to avoid using estimates, the previously described national AKI alert algorithm therefore detects possible incident cases of AKI using one of three rules. These are based on absolute or relative increases in SCr from baseline values drawn from either the previous 48 hours (Rule 1), 7 days (Rule 2), or 8-365 days (Rule 3). Despite its mandation (NHS England, 2014), 'Rule 3' of the algorithm was not however widely accepted by clinicians, mainly driven by concern that using SCr measurements dating back many months had the potential to generate false cases of AKI. The published work below aimed to examine and compare the clinical significance of alerts triggered by 'Rule 3' of the algorithm, with those triggered by 'Rule 1' and 'Rule 2'.

Moreover, while there was evidence that even small increases in SCr were associated with adverse outcomes following AKI (Kork *et al.*, 2015; Lassnigg *et al*., 2004; Newsome *et al*., 2008), it was unknown whether this applied for increases to values which occur within the population reference ranges and therefore SCr values which could be described as 'normal'. The second part of the author's study below therefore sought to evaluate the clinical significance of alerts triggered by the algorithm for SCr values occurring within the population reference range for SCr.

| | |
|---|---|
| **Title:** | **Understanding Electronic AKI Alerts: Characterization by Definitional Rules** |
| **Reference:** | **Holmes J,** Roberts G, Meran S, Williams JD, Phillips AO. Kidney International Reports. May 2017. |
| **Appendix:** | 4.1 |
| **Abstract:** | **Background/aim:** Automated acute kidney injury (AKI) electronic alerts are based on comparing creatinine with historic results. 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.<br>**Results:** A total of 47,090 incident episodes of AKI occurred between November 2013 and April 2016. Rule 1 (>26 μmol/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%, $P < 0.001$). Non-recovery 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%, $P < 0.001$).<br>**Conclusions:** 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 non-recovery. Rule 3 was the commonest cause of an alert and was associated with community-acquired AKI. |

**Evaluation of published work 12 in relation to thesis**

As measured by mode of presentation, severity of injury and outcome, the study found the clinical significance of alerts triggered by 'Rule 3' comparable to that of 'Rule 1' and 'Rule 2', and that 'Rule 3' detects the majority of all AKI, the highest proportion of stage 2 and 3 AKI, and almost 90% of AKI acquired in the community. It also found almost one in five (19.2%) alerts triggered by the algorithm are for SCr values occurring within the population reference range. Results showed that despite alerts triggered by these 'normal' SCr values represent the least severe stage of AKI, their clinical significance is statistically no different to all other AKI. From these findings, it could be concluded that although the suppression of alerts triggered by the algorithm by 'Rule

3' and/or 'normal' SCr values may minimise 'alert fatigue', the data suggests this could lead to the exclusion of a number of high risk patients.

The above conclusion should help clinicians better understand the significance of alerts transmitted by the Welsh AKI alerting system; a meaningful aim given Chang *et al*. (2011) report the acceptance of such a system relies on the end-user's confidence in its likely benefit for care and diminishes over time. From a wider perspective, this author's study could also be used to help allay speculation any healthcare providers and professionals in other areas may have regarding the clinical utility of such systems and promote their adoption elsewhere. By utilising the data set developed by the author in project one, and in the context of the overall thesis, the study is therefore demonstration of these data's potential for informing improvement in healthcare provision related to AKI.

### 4.3.2 Published work 13

**Rationale**

While the previous study focussed on the clinical utility of AKI alerts in an adult patient cohort, this next publication by the author concentrates on their functionality in a paediatric patient cohort. To detect an incident case of AKI, the previously described national AKI alert algorithm uses SCr results which date back 365 days. This approach is limited for paediatric patients in which, compared to adults, the frequency of blood tests performed is much lower, and less than 20% of paediatric inpatients reportedly undergo repeated measurements of SCr (McGregor *et al.*, 2016). To overcome this issue and in the absence of a recent SCr measurement, a number of methods for estimating baseline renal function in children have previously been proposed (Zappitelli *et al*., 2007; 2008; Atiyeh *et al*., 1996). These include back calculating a baseline SCr value from an estimated creatinine clearance (eCCl) of 120 ml/min per 1.73 $m^2$ that could be considered 'normal' (eCCl120 method) and using normative midpoint values based on age and sex related population reference ranges for SCr (NormMid method). The published work below aimed to compare the reliability of these methods for deriving SCr values with which to estimate baseline renal function in children.

Moreover, SCr-based definitions of AKI in children are further complicated by the need to consider SCr concentrations change with age and depend on body size and muscle mass. To overcome some of these issues, the previously described algorithm includes a modification for detecting AKI in patients aged less than 18 years (Table 1.3). Despite this, there was concern among some clinicians that inherent errors in the measurement of very low SCr values commonly incurred in very young children, could generate false cases of AKI, particularly in neonatal

patients. In addition, and on the basis that 0.5 mg/dL (0.03 μmol/L) is considered 'normal' in new-borns on day seven (Feldman and Guignard, 1982; Schwartz *et al*., 1984), Selewski *et al*. (2014) recommend a minimum SCr of 0.5 mg/dL (0.03 μmol/L) for diagnosis of AKI in neonates. The second part of the author's study below therefore sought to evaluate the clinical significance of alerts triggered by the algorithm for SCr values measured in neonates less than 0.5 mg/dL (0.03 μmol/L).

| | |
|---|---|
| **Title:** | **The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert** |
| **Reference:** | **Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD, Phillips AO. Kidney International. August 2017. |
| **Appendix:** | 4.2 |
| **Abstract:** | **Background/aim:** A prospective national cohort study was undertaken to collect data on all cases of pediatric (under 18 years of age) acute kidney injury (AKI) identified by a biochemistry-based electronic alert using the Welsh National electronic AKI reporting system. Herein we describe the utility and limitation of using this modification of the KDIGO creatinine-based system data set to characterize pediatric AKI.<br>**Results:** Of 1,343 incident episodes over a 30-month period, 34.5% occurred in neonates of which 83.8% were AKI stage 1. Neonatal 30-day mortality was 4.1%, with 73.3% of this being accounted for by patients treated in an Intensive Care Unit. In the non-neonatal group, 76.1% were AKI stage 1. Hospital-acquired AKI accounted for 40.1% of episodes while community-acquired AKI represented 29.4% of cases within which 33.9% were admitted to hospital and 30.5% of cases were unclassified. Non-neonatal 30-day mortality was 1.2%, with half of this accounted for by patients treated in the Intensive Care Unit. Nonrecovery of renal function at 30 days occurred in 28% and was significantly higher in patients not admitted to hospital (45% vs. 20%). **Conclusions:** The reported incidence of AKI in children was far greater than previously reported in studies reliant on clinical identification of adult AKI or hospital coding data. Mortality was highest in neonates and driven by those in the Intensive Care Unit. Nonrecovery of renal function and persistent renal impairment was more common in non-neonates and was especially high in patients with community-acquired AKI who were not hospitalized. |

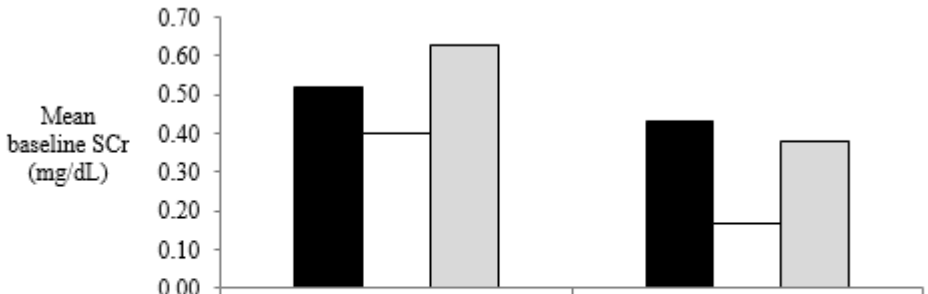
**Evaluation of published work 13 in relation to thesis**

Through observation of 1,343 episodes of paediatric AKI, the study found that while the described eCCl120 method significantly underestimates the actual baseline SCr of paediatric patients, the NormMid method more accurately estimates the actual baseline SCr of paediatric patients (Figure 4.1). Bland-Altman analysis also demonstrated significant non-agreement between estimated baseline SCr values and actual baseline SCr values. The greater unit biases (or means) seen in Figure 4.2a and c vs. 4.2b and d however confirmed that compared to the NormMid method, assuming a 'normal' eGFR of 120 ml/min per 1.73 $m^2$ is more likely to underestimate actual baseline SCr, which could lead to over-diagnosis of AKI. It could therefore be concluded that, in the absence of a recent measurement of SCr, normative midpoint values based on age and sex

related population reference ranges may offer the algorithm the most reliable method for estimating baseline renal function in children.

Of the 468 neonatal alerts analysed, the study found almost a third (33.1%) were triggered by SCr values less than 0.5 mg/dL (0.03 µmol/L). Results showed this group have significantly better outcome than all other neonatal AKI, with no association with mortality or persistent renal impairment at 30 or 90 days. Although in some cases alerts triggered by SCr values less than 0.5 mg/dL (0.03 µmol/L) may represent actual AKI in neonates, the data suggests these alerts may not be clinically significant. It could therefore be concluded that suppression of those alerts meeting such criteria would unlikely lead to the exclusion by the algorithm of high risk patients and may help minimise 'alert fatigue'.

Not only do the above conclusions help clinicians better understand the utility of alerts transmitted by the Welsh AKI alerting system for paediatric patients, they also provide potential to refine its utility further. From a wider perspective, this author's study could also be used to help allay speculation any healthcare providers and professionals in other areas may have regarding the utility of such systems for a paediatric patient cohort and promote their adoption elsewhere. By utilising the data set developed by the author in project one, and in the context of the overall thesis, the study is therefore demonstration of these data's potential for informing improvement in healthcare provision related to AKI.




| | Non-neonates | Neonates |
|---|---|---|
| ■ Actual | 0.52 | 0.43 |
| □ eCCl120 method | 0.40 | 0.17 |
| □ NormMid method | 0.63 | 0.38 |

**Figure 4.1:** Comparison of actual baseline SCr values with those derived by methods for estimating baseline renal function in children

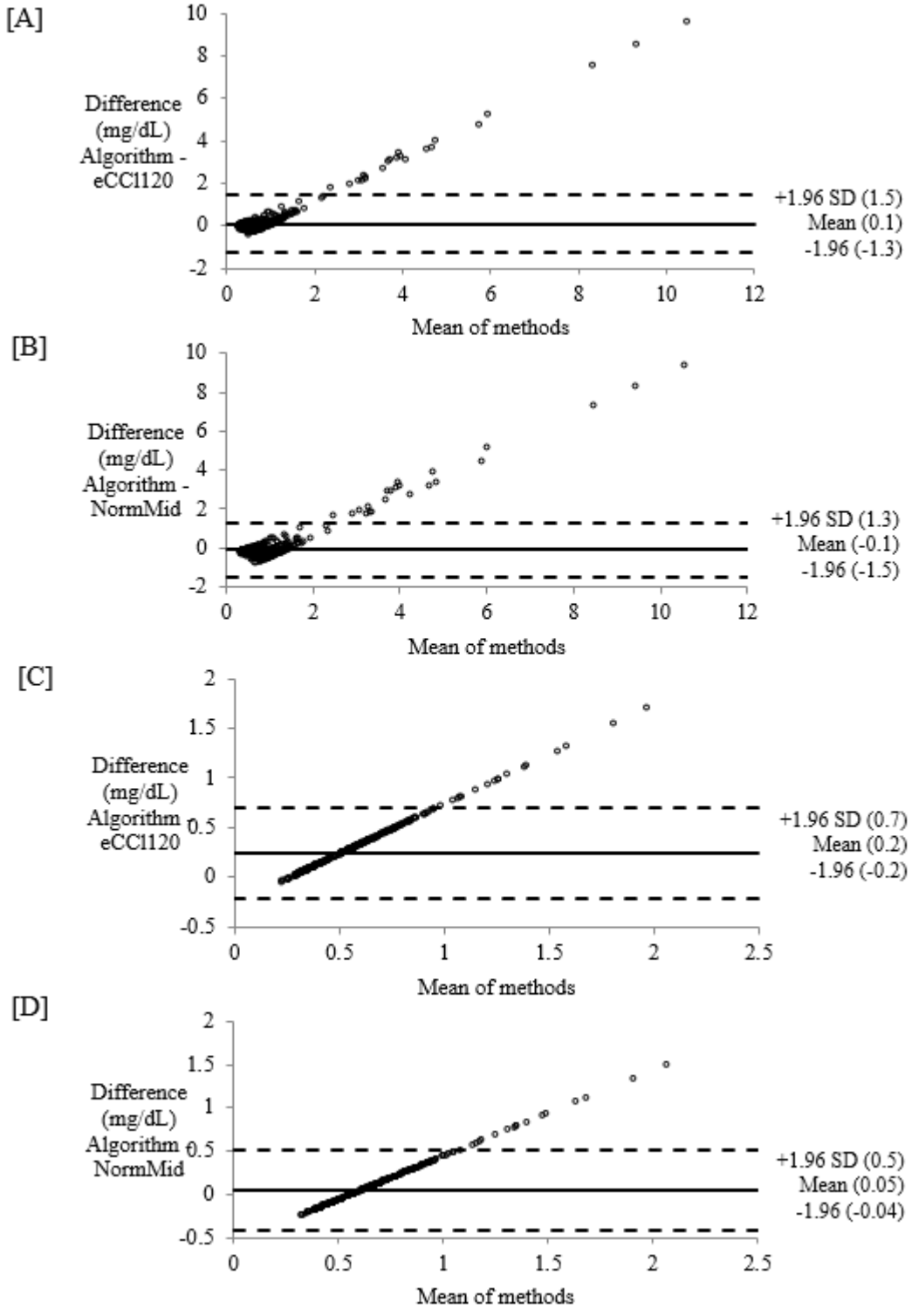



**Figure 4.2:** Bland-Altman plots comparing actual baseline SCr values with those derived by methods for estimating baseline renal function in children: [A] Actual vs. estimated creatinine clearance criteria method (eCCl120) in non-neonates [B] Actual vs. normative midpoint method (NormMid) in non-neonates [C] Actual vs. eCCl120 in neonates [D] Actual vs. NormMid in neonates

## 4.4 Development of prototype tool for QI

This section relates to the third and final objective of the project and describes the work undertaken by the author to develop a tool which, by applying the data set developed earlier in the thesis, could be used to inform QI in healthcare provision related to AKI. This work involved the:

- development of indicators which could be used to measure quality of healthcare provision related to AKI,
- identification and application of SPC techniques which could be used to analyse quality of healthcare provision related to AKI,
- consideration of AKI 'variables of interest',
- building of a prototype tool in an appropriate software, and the
- demonstration of the tool's potential for QI.

### 4.4.1 Development of AKI quality indicators

As discussed in chapter one, research on quality indicators in the field of AKI is limited. Work aimed at developing indicators to effectively measure improvement in the prevention and management of AKI is therefore regarded both a clinical and research priority (James and Pannu, 2015; Kashani *et al*., 2019; Macedo *et al*., 2020; Liu *et al*., 2020). Measurement of quality involves the development and assessment of quality indicators. These are measurements of healthcare outcome, process, or structure that can be used to measure the quality of care and identify opportunities for improvement. In their seminal paper on developing and applying quality indicators in primary care, Campbell *et al*. (2002, p.358) define a quality indicator as:

> "*statistical devices which infer judgement about the quality of care provided to populations".*

It is widely accepted that to be useful, quality indicators must be valid, reliable and feasible (Busse *et al.*, 2019). A valid quality of care indicator measures what it intends to measure and changes if quality of care changes. A reliable indicator generates similar results by different observers on different occasions and a feasible indicator is one which requires data that can be obtained at reasonable effort and cost. Some extend these characteristics further and suggest the method which is used to derive a quality indicator also determines its reliability (Campbell *et al*., 2002; Mainz, 2003a). While ideally indicators should be informed solely by rigorous empirical studies, the literature accepts this is not always possible and instead promotes the use of the best research

available, which could include scientific evidence, information on the epidemiology of the condition of interest, clinical experience-based expertise and/or guidelines. In alignment with this, the indicators developed by the author in this work are based on a combination of peer-reviewed research, including some of the author's own studies previously presented, the clinical opinion of the Welsh AKI steering group, and NICE (2014; 2019) guidelines for AKI.

While other classifications for quality of care exist, Donabedian's framework is the most widely accepted and classifies indicators as structural, process and outcome, where structure refers to information on the care setting, process refers to activities undertaken to deliver care, and outcome refers to states of health or events that follow care (Busse *et al*., 2019; Donabedian, 1988). This approach to evaluating care hypothesises that good structure increases the likelihood of good process, which in turn increases the likelihood of good outcome. Given there is limited evidence linking structure to outcomes (Brook *et al*., 2000), a combination of outcome and process indicators is recommended by most (Mainz, 2003a; 2003b). While the omission of a process-based indicator in the work here may not be ideal, these should only be measured if linked by scientific evidence to improved outcome (NICE, 2018). Others also argue that if the occurrence of what is being measured is common, and measurement of whole system performance is possible, outcome indicators are the most powerful detectors of differences in quality (Mant, 2001; Palmer 1998). Given the author's studies in project two reported high AKI incidence rates across all clinical settings in Wales, while time to respond to AKI may have offered a potential process-based indicator, the outcome-based indicators described below are proposed as the most valid, reliable and feasible.

**Indicator selection**

Using Donabedian's framework, this thesis proposes the following indicators to measure the quality of healthcare provision related to AKI in Wales:

- the rate of AKI incidence, and
- the rate of 30-day AKI associated mortality.

While the former could be used to measure the quality of care for patients at risk of developing AKI and therefore to measure improvement in the prevention of AKI, the latter could be used to measure the quality of care for patients who develop AKI and therefore to measure improvement in the management of AKI. To justify the selection of these indicators further, Liu *et al*. (2020) suggest that while post-AKI events like 30-day mortality offer a sensible metric for quality of post-AKI care, healthcare providers should also be aware of the number of patients developing AKI and who therefore warrant post-AKI care.

**Calculation of indicators**

The indicators above can be described as computer-interpretable, relying on formula based calculations, which for any given time period, could be computed as:

AKI incidence rate (per 1,000 population)
= [∑(Incident AKI episodes)/∑(Population at risk)]*1,000

30-day AKI associated mortality rate (% of AKI episodes)
= [∑(Incident AKI episodes resulting in death within 30 days)/∑(Incident AKI episodes)]*100

An important characteristic of these formulae is their conditional adaptability. While calculation of the denominator of the mortality based indicator could always remain the same, computing the incidence based indicator required dynamically considering the clinical setting of AKI being analysed. For instance, whereas HA-AKI incidence rates at individual hospitals could be reported as rates per 1,000 available hospital beds, using NHS bed data published by Welsh Government (2021), all other incidence rates could be reported as rates per 1,000 population, using Welsh population data available from the ONS.

Accuracy problems caused by missing (Sterne *et al.*, 2009) and/or unreliable data (Wells *et al*., 2013) existing in electronic health records are limitations commonly associated with electronically derived types of indicators such as those above. To overcome some of these issues, Mant (2001) suggests standardised data collection as a requirement when computing indicators, particularly outcome indicators. Following their finding that the incidence and mortality of sepsis in the United States substantially differs depending on the method of database abstraction used, Gaieski *et al*. (2013) also conclude consistent data collection methods are required for the accurate assessment of healthcare interventions and fair comparisons between healthcare providers. By utilising the data set developed earlier in this thesis, and therefore data that has been systematically collected and validated, the author proposes that the indicators developed here bypass these problems.

### 4.4.2 Consideration of AKI 'variables of interest'

'Simpson's Paradox' refers to the disappearance of trends in groups of data when groups are inappropriately combined (Simpson, 1951). This statistical phenomenon can affect the results of both comparative and non-comparative analyses. Overcoming it involves limiting the effect of differences between groups on such analyses and can be achieved by the grouping or splitting of data for which an indicator measures. This is otherwise known as data stratification.

**Data stratification**

The scale and scope of the data set developed by the author earlier in this thesis is such that it enables the data on the indicators developed here to be stratified in multiple ways. While theoretically this could include filtering by any field in the described data set (Table 2.1), the work presented here primarily concerns the splitting of these data by the following strata (and stratums):

- clinical setting of AKI (all-cause AKI, HA-AKI or CA-AKI),
- severity of AKI (Stage 1, 2 and/or 3),
- local health board (for which there are 7 in Wales),
- hospital (for which there are 19 in Wales),
- clinical specialty (for which there are 86 listed in the WLIMS), and
- for HA-AKI only:
    - ward location (for which there are >1000 listed in the WLIMS), and
- for CA-AKI only:
    - primary care cluster (for which there are 64 in Wales) and/or
    - GP practice (for which there are approximately 400 in Wales).

While not all of the above may necessarily feature as 'variables of interest' in the forthcoming sample SPC charts presented by the author below, their exclusion here does not suggest they have no place in future work. Moreover, while some of the more lower level data above may have the potential to provide more granular information, Mainz (2003a) suggests outcome indicators become less useful as the number of data points reduces and the perspective narrows. The prototype tool developed by the author here is therefore predominantly proposed as a 'national' tool, intent on measuring high-level performance, mostly at the provider level.

### 4.4.3 SPC methodology

While quality indicators represent 'what' is measured, QI methodology refers to 'how' quality is measured. Influenced by the work of the statistician Shewhart, Deming (1986), a management philosopher and leading thinker in quality theory, postulates that variation exists in all processes and can be controlled (natural or common-cause) or uncontrolled (unnatural or special-cause). Traditional quality management theory states that a systematic approach which reduces process variation is essential for optimising process and outcome (Anderson *et al*., 1994). This industrial notion of quality transfers to healthcare in which The Health Foundation (2021) suggest two types of variation exist: variation in system processes, and variation in clinical practice, where the former can lead to inefficiency and waste, and the latter can result in error and harm.

Statistical process control (SPC) methods are central to most QI methodology. Through scientific analysis of data on quality indicators over time, these techniques enable the identification and investigation of variation in quality, and can therefore be used to evaluate the impact of, and identify opportunities for, QI. As potential tools to inform QI in healthcare provision related to AKI, this thesis explores the following SPC techniques:

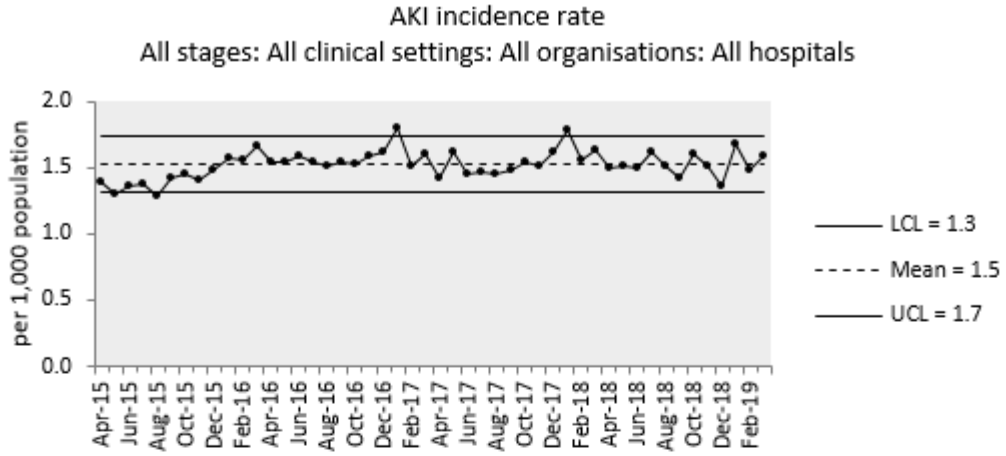
- control charts,
- funnel plots, and
- Pareto charts.

**Control charts**

Control charts are a primary SPC tool routinely used to monitor quality over time (Benneyan *et al*., 2003). A main benefit of the control chart is its visual nature which allows users to easily understand the range and consistency of what is being measured over time (Sebastian-Coleman, 2013). The charts take the format of graphs which plot data points in chronological order against the mean and upper (UCL) and lower control limits (LCL) of the data set concerned. These control limits reflect the expected variation in the data and are typically defined as three standard deviations (SD) from the mean. While data points falling within these limits are consistent with natural or common-cause variation, points falling outside of these thresholds significantly differ from the mean by more than could be expected by chance and therefore represent unnatural or special-cause variation which may warrant further investigation. The Institute for Healthcare Improvement suggest that by applying a number of other principles, the control chart can also be used to identify 'shifts' and 'trends' in the data it plots. While the former is indicated by six or more consecutive points above or below the mean, the latter is indicated by five or more consecutively increasing or decreasing points (Martin *et al*., 2016).

Although a simple run chart may offer an alternative method for monitoring data on quality over time, this thesis proposes the control chart as the more robust. While such charts could be used to identify unnatural variation in quality of healthcare provision related to AKI in Wales over time, they could also be used to evaluate the impact of interventions aimed at improving quality of healthcare provision related to AKI in Wales. Figure 4.3 shows control charts created by the author which plot data on the two earlier AKI quality indicators. While these example charts plot national all-cause AKI incidence and mortality rates, similar charts are also producible for other variables which may be of interest, including any combination of those listed in Section 4.42. Moreover, while the plots in Figure 4.3 are based on monthly time series data, also possible are similar plots based on the analysis of quarterly time series data.

[A]

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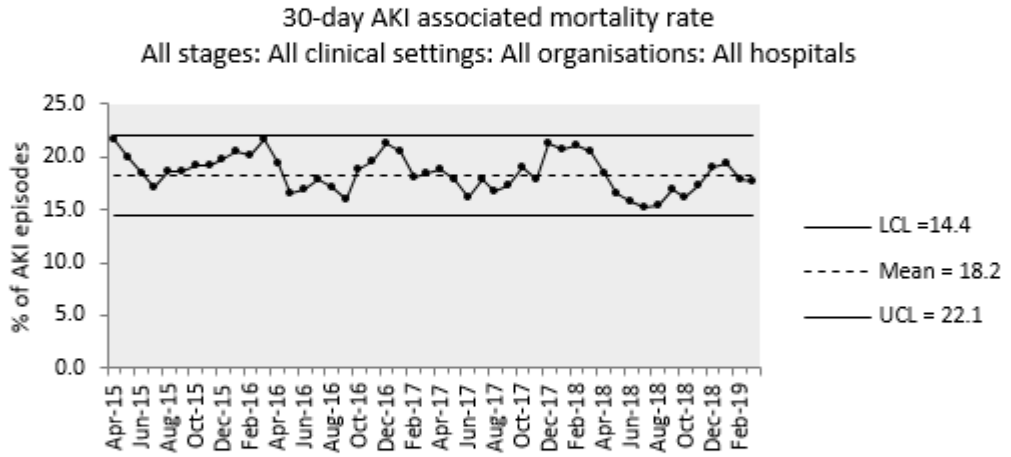


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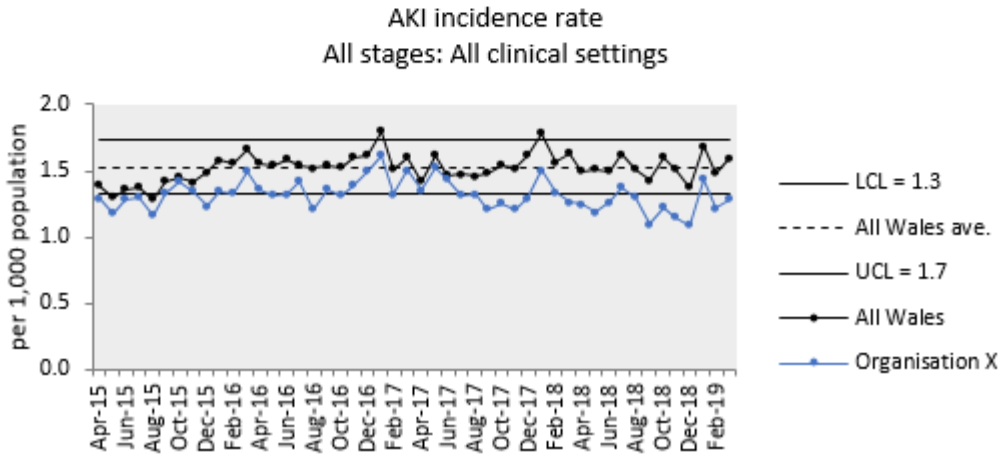



**Figure 4.3:** Sample control charts developed by the author to monitor quality of healthcare provision related to AKI: [A] AKI incidence rate per month [B] 30-day AKI associated mortality rate per month [C] AKI incidence rate for a selected variable of interest vs. all Wales AKI incidence rate

**Benchmarking**

Data on quality indicators serve many purposes. They make it possible for healthcare providers to measure, document and demonstrate quality of care and enable the comparison of performance between providers, areas, and in some cases, countries. These comparisons, otherwise known as the method of benchmarking, are proven to be effective for identifying opportunities for improvement (Kiefe *et al*., 2001) and reducing variation in care (Ettorchi-Tardy *et al*., 2012). In their seminal paper on clinical governance models, Scally and Donaldson (1998) depict (Figure 4.4) how, through benchmarking, spreading good practice found at exemplar organisations can improve quality at others.

The basic principle of benchmarking involves identifying a point of comparison, a benchmark, against which everything else can be compared. This can be based on either external or internal criteria. Whereas the former uses research and/or expert judgement to establish a minimum level of performance, an internal benchmark is calculated from within the data set itself and usually involves using the overall average to define the expected level of performance. Given research on AKI care standards is limited (Macedo *et al*., 2020), the work here adopts an internal benchmark, defined as the national all Wales mean.

**Funnel plots**

While overlaying the data of a selected variable of interest onto the all Wales mean using a control chart offers a form of benchmarking (Figure 4.2c), this method is not suitable for easily and simultaneously comparing multiple data series. A funnel plot is an alternative SPC technique commonly used to compare and graphically illustrate variation in quality between healthcare providers, to identify those with significantly better or worse performance.

For a selected time period, these graphs plot a quality indicator of interest on the y axis, against the sample size of each sub-population that is being compared on the x axis. Alongside a line drawn at the population mean (or benchmark), they also include lines drawn at 95% and 99.8% control limits. Because they vary with sample size, these limits also give rise to the chart's characteristic 'funnel' shape and while the former equates to a conceptual confidence limit of 95%, which statistically translates to 2SD from the mean and a significance level of $p<0.05$, the latter equates to a conceptual confidence limit of 99.8%, which statistically translates to 3SD from the mean and a significance level of $p<0.001$. Data points falling outside of these thresholds can be described as outliers, which significantly differ from the mean by more than could be expected by chance and therefore represent unnatural or special-cause variation. In the case of this work, such points could represent rates of AKI incidence and/or mortality which significantly differ

from the national all Wales mean by more than could be expected by chance, and which therefore may warrant further investigation.

The control limits calculated in the work here can be described as coming from the Poisson distribution, which applies to phenomena expressed as crude rates, ratios or proportions, which can be defined as the number of events in a fixed population over a selected period of time (Clopper and Pearson, 1934; Spiegelhalter, 2005). Calculation of such limits involves computing a Z score for each data point that is plotted which statistically can be defined as the number of standard errors between the sub-population's mean and the population mean. In more straightforward terms, it indicates how far the two means are away from each other. Where x is the rate of the sub-population being compared, μ is the population mean, and σ is the population SD:

$$Z = (x - \mu) / \sigma$$

Figure 4.5 shows funnel plots created by the author which plot data on the two earlier AKI quality indicators. While these example charts compare the rates of HA-AKI incidence and mortality at different local health boards and hospitals, similar charts are also producible for other variables which may be of interest. This could for instance include plotting by ward location or clinical specialty within individual hospitals, or for CA-AKI, plotting by primary care cluster and/or GP practice either for all of Wales or within individual local health boards. Moreover, while the plots in Figure 4.5 are based on data for a quarterly time period, also possible are similar plots based on the analysis of longer or shorter time periods, such as years or months.

**Limitations of funnel plots**

The funnel plot is not without some limitations. A first relates to its control limits, which in some cases have the potential to incorrectly identify 'false-positive' outliers. At approximately one in a thousand for 99% control limits, and 25 in a thousand for 95% control limits, the risk of these so-called 'Type 1 errors' is however very low.

Although it may allow for additional variability expected in smaller samples, another limitation of the funnel plot is the potential for samples which extremely differ from others to skew the overall benchmark to which all others are compared. In the context of the work here, this could translate to the skewing of the national mean by an atypically small hospital, or an atypical provider organisation such as Powys Teaching Health Board, which has no district general hospitals, is served by laboratories in neighbouring health boards, and provides healthcare services for a very small proportion of the Welsh population. While exclusion of these relatively

different samples could overcome this issue, guidance by the ONS (2013) also suggests data points relating to less than 10 events should also be excluded from analyses.

Another common issue associated with funnel plots is over-dispersion, whereby an abundance of points sit outside of the control limits. This can arise when large numbers of events are plotted and case-mix or other risk factors have not been accounted for (Spiegelhalter, 2005). Given it is known that multiple confounding factors, other than care, can contribute to patient outcomes, some recommend controlling for differences in case-mix when evaluating quality indicators (Busse *et al*., 2019; Iezzoni, 1996; Mainz 2003a). This is described as risk-adjustment and can be used to overcome potential over-dispersion manifesting in funnel plots.

**Risk-adjustment**

Risk adjustment models can include covariates such as patient demographics, comorbidities, lifestyle factors, and the severity of the illness that is the focus of measurement (Dover and Schopflocher, 2011). The author's studies presented in project two of this thesis suggest any potential over-dispersion which may be present in the funnel plots in Figure 4.5 may represent factors such as age or social deprivation. Age-standardisation is a commonly used risk adjustment technique and while artificial population structures like the European Standard Population (ESP) can be used to weight incidence and mortality data and produce age-standardised rates (ASRs) (ONS, 2014; WHO, 2013), particularly when making international comparisons, deriving an age correction factor from within the data being analysed is another method. To demonstrate how the 30-day AKI associated mortality rate indicator described in this work could be age-standardised, the author used Cox proportional-hazards regression modelling in IBM SPSS. This modelling resulted in a 0.034 per year age correction factor for AKI in all clinical settings, 0.029 for HA-AKI and 0.050 for CA-AKI. Where a sub-population could represent a local health board and/or hospital in Wales, these factors could be applied to standardise the rate of each sub-population as follows; where x represents the mean age of the sub-population being compared, and μ represents the mean age of the overall population:

ASR of 30-day AKI associated mortality
= 30-day AKI associated mortality rate + [(x - μ)*(1+age correction factor)]

The funnel plots in Figure 4.6 show the results of this preliminary risk-adjustment work and demonstrate how fewer points, which in this case are Welsh hospitals, fall outside of the control limits once the data is corrected for age, which could represent less over-dispersion.

While some literature suggests risk adjustment creates a so-called 'level playing field' and therefore regards controlling for factors beyond the health system essential for fair comparison of outcomes across providers, others suggest these underlying sources of variation are likely of interest to providers. Flowers (2009, p.7) suggests that "r*ather than eliminate them, we should draw attention to them*". This school of thought is also the stance taken in this thesis, justified by the view that healthcare provision related to AKI in Wales should be the same for every patient nationwide. Not risk-adjusting also allows for confounding factors to, in some cases, help explain instances of outlying performance following further analysis.

**Alternative benchmarking methods**

Following the described limitations which can be associated with funnel plots, the author also explored caterpillar plots and league tables as potential tools for benchmarking the quality of healthcare provision related to AKI in Wales (Figure 4.7). Unlike the funnel plot, caterpillar plots simply plot individual means against each other and do not plot the overall mean. Mohammed and Deeks (2008) suggest presenting data simultaneously like this has the potential to spuriously rank providers. The same is also true for ranking organisations in league-like tables (Goldstein and Spiegelhalter 1996). Allwood *et al*. (2013) also report that when presenting institutional comparisons, clinicians favour the funnel plot over these alternative methods.

This thesis therefore proposes the funnel plot as the most robust and reliable SPC technique to benchmark and identify outlying quality of healthcare provision related to AKI in Wales. Such charts could be used to identify instances of both low and high relative quality. They could therefore be used to identify those areas in Wales with most need and/or potential for QI, and also help facilitate the spread of good or best practice from particularly high performing areas to areas where performance is suboptimal.

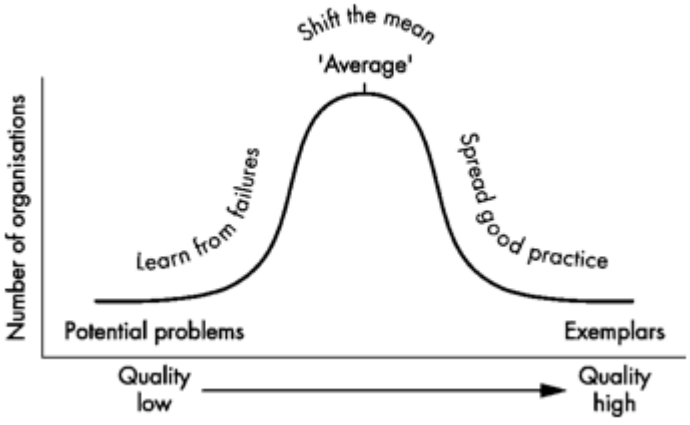



**Figure 4.4:** The quality in healthcare 'variation curve' *(Adapted from Scally and Donaldson, 1998)*

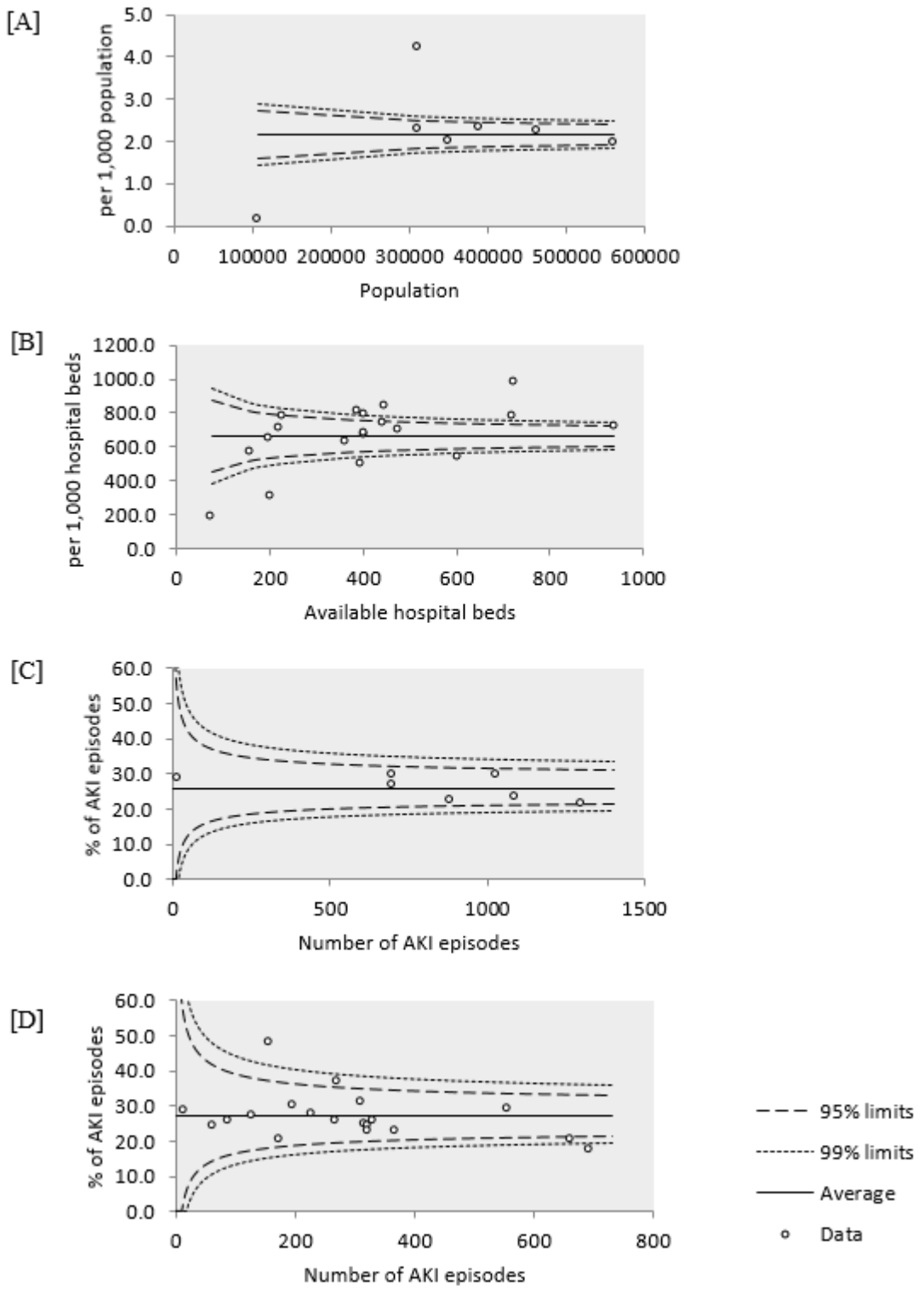



**Figure 4.5:** Sample funnel plots developed by the author to compare quality of healthcare provision related to AKI: Comparison of HA-AKI incidence rates at local health boards [A] and hospitals [B]. Comparison of 30-day HA-AKI associated mortality rates at local health boards [C] and hospitals [D]. *The upper and lower bounds of the Poisson distribution for the funnel plots presented in [C] and [D] were calculated using Visual Basic programming routines made available by Pezzullo (StatPages, 2021). These show how control limits can be estimated for hypothetical population sizes starting from zero and results in more 'smoothed' looking funnels compared to those in [A] and [B].*

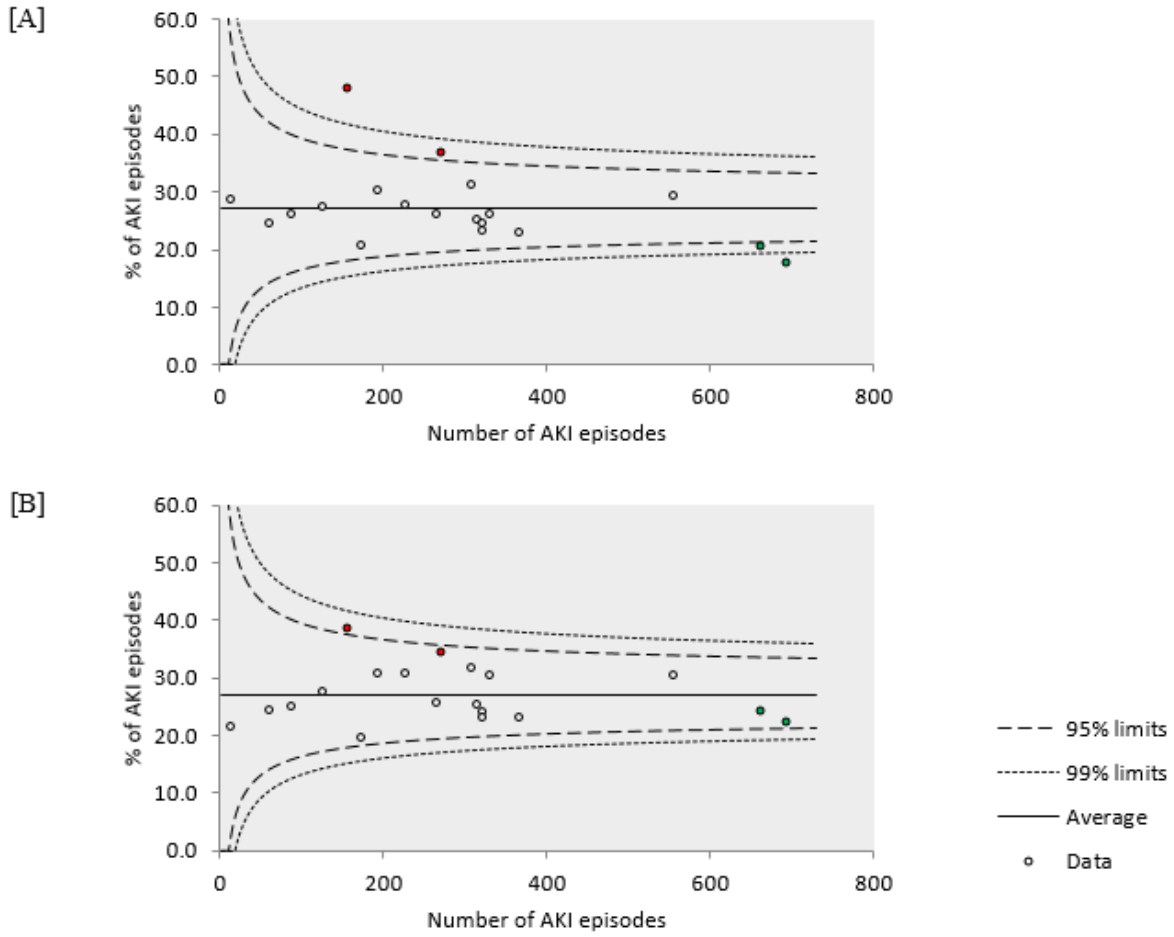
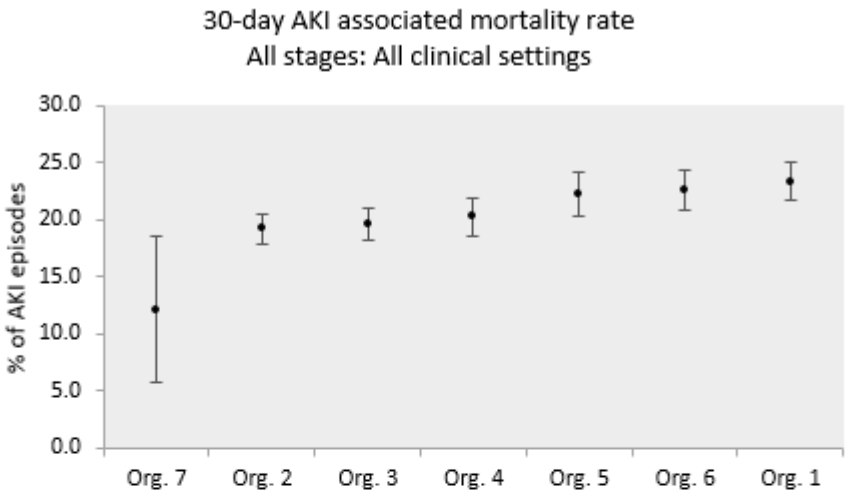



**Figure 4.6:** Sample funnel plots developed by the author to show the effect of risk-adjusting data on AKI quality indicators for age: Comparison of 30-day HA-AKI associated mortality rates at hospitals using risk-adjusted data [A] and non risk-adjusted data [B]. P*oints highlighted red and green indicate hospitals in which the average age of patients was respectfully higher and lower than the average age in the whole data set. These demonstrate how the mortality rates at these hospitals move closer to the average following adjustment for age.*

[A]




[B]

| | Year X | | | |
|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** |
| Org.1 | 23.3% | 18.5% | 17.7% | 22.2% |
| Org.2 | 19.2% | 16.6% | 16.7% | 18.7% |
| Org.3 | 19.6% | 17.4% | 17.1% | 20.4% |
| Org.4 | 20.3% | 16.6% | 17.6% | 18.2% |
| Org.5 | 22.2% | 19.7% | 17.2% | 19.9% |
| Org.6 | 22.6% | 18.4% | 16.4% | 20.4% |
| Org.7 | 12.2% | 8.1% | 8.5% | 17.4% |
| **All Wales average** | **20.9%** | **17.6%** | **17.1%** | **19.9%** |

**Figure 4.7:** Sample caterpillar plots [A] and league tables [B] developed by the author to compare 30-day AKI associated mortality rates. *Error bars indicate 95% confidence limits. Rates highlighted red are above the average for all Wales.*

**Pareto charts**

While funnel plots could be used to identify instances of outlying quality of healthcare provision related to AKI in Wales, this thesis proposes the Pareto chart as a SPC technique which could be used to investigate potential causes of these instances of outlying quality of healthcare provision related to AKI.

Based on the 'Pareto principle', which states 80% of outcomes result from 20% of causes and is otherwise known as '80/20 rule' or the 'law of the vital few' (Juran, 1986), Pareto charts are common tools used in QI for decision making and prioritising areas for improvement and/or inquiry. These charts take the format of bar graphs, and by plotting both the frequency and cumulative frequency of an event against a selected variable of interest, can be used to effortlessly identify factors associated with the most, or highest proportions of an event.

Figure 4.8 shows Pareto charts created by the author which plot data on the two earlier AKI quality indicators. Unlike SPC charts previously presented, the y axes in these charts plot AKI incidence and mortality as crude numbers, not rates i.e. number of incident AKI episodes and number of deaths within 30 days of an incident AKI episode. While the example charts in Figure 4.8 rank national HA-AKI incidence and mortality by clinical specialty, similar charts are also producible for any other variable which may be of interest, including any of those listed in Section 4.42. It could also include plotting by other more exciting lower level data, which is not necessarily related to the care provider and/or location of care, such as patient age and/or socioeconomic status, and day of the week and/or time of day AKI is detected. Moreover, while the plots in Figure 4.8 are based on data for a quarterly time period, also possible are similar plots based on the analysis of longer or shorter time periods, such as years or months.

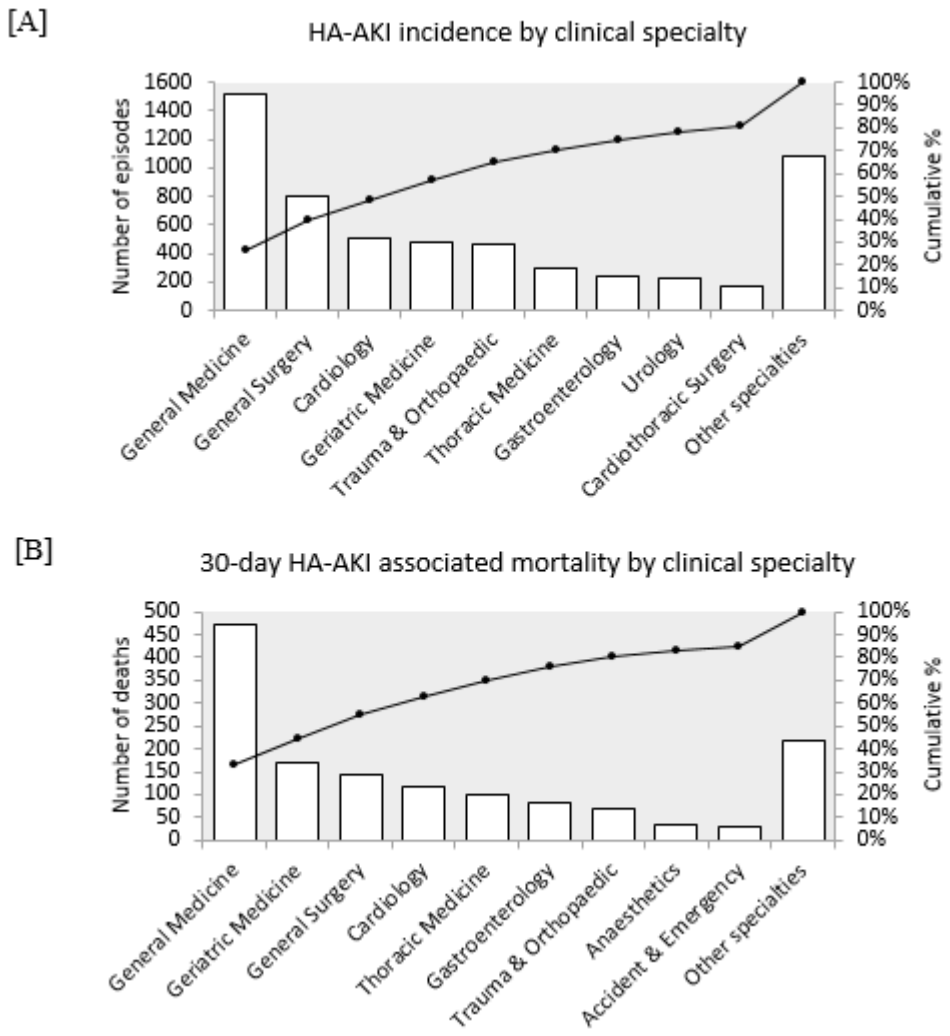



**Figure 4.8:** Sample Pareto charts developed by the author to investigate potential causes of outlying quality of healthcare provision related to AKI: [A] Number and % of HA-AKI incident episodes by clinical specialty [B] Number and % of 30-day HA-AKI associated deaths by clinical specialty

### 4.4.4 Software selection

Built in 'Microsoft Excel' software, Appendix 4.3 provides screenshots of the prototype tool developed by the author which could be used to inform QI in healthcare provision related to AKI in Wales. These show how in addition to separate 'Control charts', 'Funnel plots' and 'Pareto charts' tabs, the tool also includes a 'Home', 'Glossary' and 'Description of methods' page. The SPC charts created use Visual Basic programming macros to automatically adjust the data (and titles) they display according to selections made in the dropdown menus. These dropdown menus also apply dynamic validation rules to prevent inappropriate selections by end-users. For example, the control chart is only filterable by an individual hospital if HA-AKI is selected as the clinical setting. The graphical display included in the funnel plot tab is accompanied by a conditionally formatted table which highlights areas of high and low relative performance.

Presented only as a prototype, the author acknowledges that future versions of the tool may benefit from development in more advanced and/or web-based softwares and applications. Examples of such softwares, which offer added functionality such as faster processing times and online publishing facilities, include 'Tableau' and 'Power BI', with the latter in routine use at most NHSW organisations at time of writing.

### 4.4.5 Demonstration of tool for QI (Published work 14)

To demonstrate the potential of the tool developed here for QI, and to strengthen the proposal for its potential widespread and routine adoption, the author offers the following published work.

| | |
|---|---|
| **Title:** | **Acute kidney injury demographics and outcomes: changes following introduction of electronic acute kidney injury alerts - an analysis of a national dataset** |
| **Reference:** | **Holmes J**, Donovan K, Geen J, Williams JD, Phillips AO. Nephrology Dialysis Transplantation. June 2020. |
| **Appendix:** | 4.4 |
| **Abstract:** | **Background/aim:** Electronic alerts for acute kidney injury (AKI) have been widely advocated. Our aim was to describe the changes in AKI demographics and outcomes following implementation of a national electronic AKI alert programme.<br>**Methods:** A prospective national cohort study was undertaken to collect data on all cases of AKI in adult patients (≥18 years of age) between 1 April 2015 and 31 March 2019.<br>**Results:** Over the period of data collection, there were 193 838 AKI episodes in a total of 132 599 patients. The lowest incidence of AKI was seen in the first year after implementation of electronic alerts. A 30-day mortality was highest in Year 1 and significantly lower in all subsequent years. A direct comparison of mortality in Years 1 and 4 demonstrated a significantly increased relative risk (RR) of death in Year 1: RR = 1.08 [95% confidence interval (CI) 1.054–1.114 $P < 0.001$]. This translates into a number needed to treat in Year 4 for one additional patient to survive of 69.5 (95% CI 51.7–106.2) when directly comparing the outcomes across the 2 years. The increase in the number of cases and improved outcomes was more pronounced in community-acquired AKI, and was associated with a significant increase in patient hospitalization.<br>**Conclusions:** This study represents the first large-scale dataset to clearly demonstrate that a national AKI alerting system which highlights AKI is associated with a change in both AKI demographics and patient outcomes. |

By analysing and comparing the incidence and outcome of AKI over a four year period, this author's study sought to explore whether implementation of the AKI alerting system described in this thesis was associated with changes in the number of patients in Wales developing AKI and/or changes in outcome following AKI. The study, which involved observation of 132,599 patients with AKI, found AKI incidence rates were lowest, and 30-day AKI associated mortality rates were highest, in the first year following introduction of the AKI alerting system described in this thesis. It was also able to demonstrate that the increases in incidence and the improvements in

outcome observed in the three subsequent years were more pronounced in CA-AKI compared to HA-AKI.

While this study focusses on electronic alerts as the QI intervention, by employing techniques and indicators similar to those applied by the tool developed by the author above, it is example of the tool's potential to evaluate further national QI initiatives aimed at improving healthcare provision related to AKI in Wales. By utilising the data set developed by the author in project one, and in the context of the overall thesis, the study is also additional demonstration of these data's potential for informing improvement in healthcare provision related to AKI.

### 4.5 Summary of project

In addressing the third and final aim of the thesis, this final project has presented a number of practical examples of work by the author to demonstrate the potential of national data on AKI alerts, and therefore routine SCr data, for QI in healthcare provision related to AKI. By utilising the novel data set developed by the author in project one, this work has involved:

1. Two peer-reviewed publications by the author which explored opportunities to refine the algorithm of the Welsh AKI alerting system. These studies conclude:

    - alerts triggered by 'Rule 3' and/or 'normal' SCr values are clinically significant and although their suppression by the algorithm may minimise 'alert fatigue', this could lead to the exclusion of a number of high risk patients,
    - alerts triggered for neonates by SCr values less than 0.5 mg/dL (0.03 µmol/L) may not be clinically significant and their suppression by the algorithm would unlikely lead to the exclusion of high risk patients and may therefore help minimise 'alert fatigue', and
    - in the absence of a recent measurement of SCr, normative midpoint values based on age and sex related population reference ranges may offer the algorithm the most reliable method for estimating baseline renal function in children.

    These conclusions demonstrate the clinical significance of alerts transmitted by the Welsh AKI alerting system and also have the potential to further refine its clinical utility. From a wider perspective, these author's studies could also help to allay any speculation healthcare providers and professionals elsewhere may have regarding the value of such systems and encourage their adoption in other areas.

2. Development of a tool by the author which could be used to robustly and reliably inform QI in the prevention and/or management of AKI in Wales, and which proposes the adoption of:

    - the rate of AKI incidence and rate of 30-day AKI associated mortality as indicators to measure quality of healthcare provision related to AKI, and
    - the following SPC techniques to analyse, and identify and investigate variation in, quality of healthcare provision related to AKI:
        - control charts,
        - funnel plots, and
        - Pareto charts.

    In doing so, the described tool provides a means to identify opportunities for, and evaluate the impact of, QI in healthcare provision related to AKI in Wales, a mechanism which did not exist prior.

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## Appendices

**Appendix 1.1:** Patient safety notice for Acute Kidney Injury (PSN029) issued by Welsh Government in 2016

# Patient Safety Notice

**PSN 029 / March 2016**

GIG CYMRU NHS WALES

Llywodraeth Cymru
Welsh Government

## Standardising the early identification of acute kidney care

**To:** All NHS Chief Executives, Medical Directors, Directors of Nursing and Patient Safety Teams.

Acute Kidney Injury (AKI) is characterised by an abrupt loss of kidney function and is strongly associated with high mortality and morbidity. Reported incidence of AKI varies depending on the definition, clinical setting and the population studied. In hospital incidence reports varying between 4 and 18% of all admissions, with an incidence as high as 70% reported for critically ill patients.

The Welsh AKI Steering Group has confirmed that there remains no validated risk assessment tool in use across the UK and that local studies have shown that the prevalence of accepted risk factors is so high in patients acutely admitted to hospital, there is no evidence to support the fomal undertaking of a scoring/risk assessment.

To support clinical management of acutely unwell patients, All-Wales AKI guidelines have been developed by the Steering Group and these are supported by an electronic alert (E-alert) system. This has been implemented across all LHBs in Wales. The system creates an alert message to blood results where an abnormal Creatine has been recorded which can indicate AKI.

The following set of rules trigger the Laboratory Information Management System (LIMS) to send out an associated alert message to highlight the possibility of AKI to the requesting clinician:

| Rule | Trigger | Associated alert |
|---|---|---|
| Rule 1 | >26µmol/L increase in creatinine within 48hrs | *Acute Kidney Injury alert: rising creatinine within last 48 hours.* |
| Rule 2 | >50% increase in creatinine within 7 days | *Acute Kidney Injury alert: rising creatinine within last 7 days.* |
| Rule 3 | >50% increase in creatinine against median result 8-365 days | *Acute Kidney Injury alert: creatinine has increased over median value from past year; consider also progressive CKD.* |
| Rule 4 | No index value available from past year but creatinine above reference range | *Raised creatinine: if not known CKD suggest repeat to rule out Acute Kidney Injury.* |

## Actions

**Who:** All providers of NHS funded care

**When:** As soon as possible and no later than 8 April 2016.

1. Distribute this Notice to all relevant staff who are involved in the provision of acute care in all settings including hospitals, primary care, emergency departments and Medical and Surgical Assessment Units.
2. Consider if immediate action needs to be taken locally.
3. Each LHB and Trust should work with the AKI Steering Group to have a plan to improve management of AKI across community and hospital setting. This work should be reported to board level through existing quality and safety mechanisms.
4. Share any learning from local investigations or locally developed good practice resources through the LHB AKI Champion to the AKI Steering Group.

**Share any learning from local investigations or locally developed good practice resources by emailing:** ImprovingPatientSafety@Wales.GSI.Gov.UK



Queries should be sent to: **ImprovingPatientSafety@Wales.GSI Gov.UK**
**www.patientsafety.wales.nhs.uk**

The established e-alert contains a link to the national AKI treatment guidelines for reference. The combination of alert and guidelines will provide benefits for both helping clinicians identify that an episode of AKI has occurred and the necessary action to treat.

It is expected that local data collection and the learning from this will be discussed at relevant mortality and harm governance meetings.

The AKI Steering Group has a Database which is prospectively collecting the incidence, activity and outcomes of AKI across primary and secondary care in Wales. This will provide a baseline assessment and develop clinical strategies to improve the management of AKI.

## Stakeholder Engagement

The AKI Steering Group is chaired by Professor Aled Phillips and is hosted and supported by the Welsh Renal Clinical Network. The Steering Group comprises 'AKI Champions' from each Health Board, Trust and other organisations in Wales.

**Appendix 1.2:** National AKI care guidelines developed by the Welsh AKI steering group

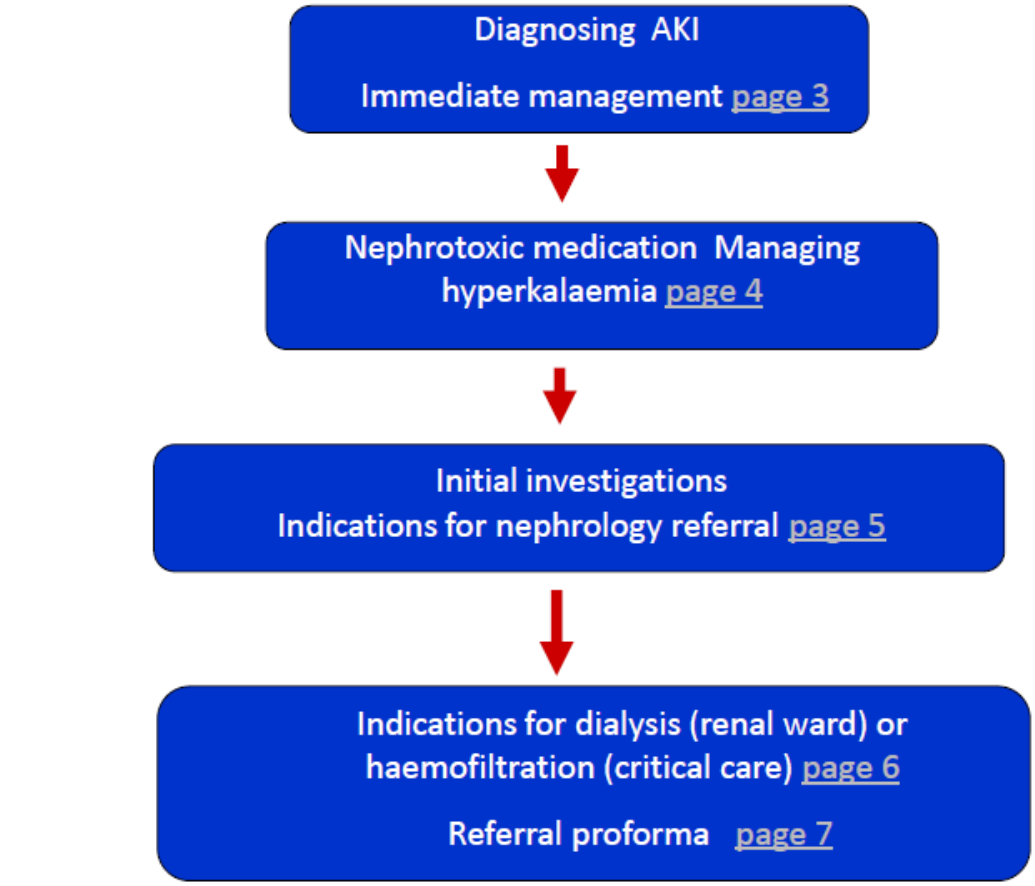
Rhwydwaith Clinigol Arennol Cymru
Welsh Renal Clinical Network

# Acute Kidney Injury Welsh Clinical Guidelines

**Author: National AKI Steering Group**

**Published May 2014**

# Overview of Guidelines




Special Circumstance

AKI in cirrhotics

Rhabdomyolysis

Renal transplant patients page 8

Contrast nephropathy page 9

## Diagnosis and immediate management

**Acute kidney Injury (AKI) is an abrupt reduction in kidney function. The KDOQI (2012) definition of AKI is shown below Most cases will be diagnosed on the basis of a rapid rise in serum creatinine. Once diagnosed, AKI must be managed PROMPTLY to avoid further injury**

### AKI definition

- Increase in creatinine to >1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

**OR**

- Increase in creatinine by >26.5 µmol/l within 48 hours

**OR**

- Urine volume <0.5 ml/kg/h for 6 hours.

### Immediate Management of AKI

- Assess fluid status (JVP/BP/HR/Cap refill time)
- If clinically dry, rehydrate e.g 250-500ml fluid boluses with timely assessment of response (BP/Urine output/JVP). If no response to 2L of fluid, senior or critical care review.
- TREAT SEPSIS EARLY (antibiotics and fluids within 1 hour)
- Manage hyperkalaemia (see page 4)
- Withhold potentially nephrotoxic drugs until senior review (see page 4)
- Examine for urinary retention
- Monitor fluid input and output (consider urinary catheter insertion)
- ENSURE A ROBUST HANDOVER TAKES PLACE SO THAT THE PATIENT CONTINUES TO BE CLOSELY MONITORED (ESPECIALLY OUT OF HOURS)

## Review Drug Chart

| Potentially Nephrotoxic | Side Effects Exacerbated by AKI |
|---|---|
| •ACE inhibitors e.g. Ramipril ( ↑$K^+$)<br>•Angiotensin Receptor Blockers e.g. Losartan ( ↑$K^+$)<br>• Spironolactone, Epleronone, Aliskiren, Amiloride ( ↑$K^+$)<br>• NSAIDs ( ↑$K^+$)<br>• Trimethoprim ( ↑$K^+$)<br>• Aminoglycosides e.g. Gentamicin<br>• Furosemide/Bendroflumethazide/Metolazone (IF clinically dry) | Metformin<br>Opiates |

**ACE inhibitors / ARBs are prone to cause AKI/hyperkalaemia in diabetics, vasculopaths and the elderly, particular under conditions that predispose to dehydration such as diarrhoea, infection, CVA. If unsure, withold and consider prescribing in the evening once subsequent blood results have been reviewed by senior.**

### Management of Hyperkalaemia ($K^+$>6.4 or ECG changes)

- Ensure patient has cardiac monitoring
- Review medication chart (see above)
- IV Calcium Gluconate (10ml of 10% over 10 mins IV) to stabilise myocardium (can be repeated if ECG changes persist).
- IV Insulin (rapid acting preparation) + Dextrose (e.g. 10 Units Actrapid in 50ml of 50% Dextrose) over 20 mins. NB: Effect seen within 15 minute, lasts up to 4hrs. (Check Blood glucose following infusion – risk of hypoglycaemia)
- Nebulised salbutamol will reduce potassium, but use with care if underlying IHD or patient is tacycardic
- If venous bicarbonate <22 give IV Sodium bicarbonate (1.26%) e.g 500ml over 1-2 hr (depending on fluid status of patient). NB: may exacerbate fluid overload, thus caution if CCF/oedema

**Ultimately potassium removal from the body is dependant on urinary clearance. If a patient is persistently oligo/anuric with hyperkalaemia they are likely to require renal support and should be discussed with the renal team (see below)**

## Initial Investigations of AKI

- Assess acid base status - venous Bicarbonate OR if haemodynamically unstable ABG (+ Lactate)
- FBC (If low platelets -consider HUS/TTP )
- USS KUB (if suspicion of obstruction or cause of AKI not apparent). Perform within 6h if single kidney or high suspicion of obstruction, otherwise within 24h . All AKI with evidence of obstruction should be discussed with Urology.
- CK if symptoms/history suggest risk of rhabdomyolysis
- Dipstick urine (AND document results)
- If proteinuria on dipstick, send sample to lab for urine Protein/Creatinine ratio. To estimate 24h urinary losses, multiply result by 10 to approximate 24h losses e.g. (if result in mg) PCR 140mg/mmol = 1400mg in 24h (1.4g)
- Myeloma screen (plasma and urine electrophoresis – if appropriate)
- Urgent autoantibody screen (ANA, C3,C4, ANCA, Anti-GBM) if possibility of glomerulonephritis (only if blood and protein on dipstick)
- Consider toxicology screen if significant unexplained acidosis (e.g. ethylene glycol toxicity)

## Patients who should be discussed with Nephrology

- Any unexplained and deteriorating AKI
- Possible glomerulonephritis (blood and protein on dipstick)
- Possible autoimmune disease e.g. history of nasal/sinus symptoms, arthralgia, rash, pulmonary renal syndromes
- Patients who are likely to need renal replacement therapy (see page 6)
- ALL renal transplant patients (see page 8)
- ALL dialysis patients with hyperkalaemia/fluid overload

Use referral proforma (page 7)

# Renal Replacement Therapy (RRT)

**If managed appropriately the majority of AKI is reversible, however a small number of patients will require renal replacement therapy (RRT). Haemodialysis is provided on the renal unit, haemofiltration is provided in critical care. In general, patients with AKI will fall into 2 categories - those with single organ failure and those with AKI as part of a multi organ disease process (such as sepsis). Some patients will be too unstable to transfer to the renal unit (see below). Prior to initiating discussions with either nephrology or critical care about renal replacement therapy, a decision should be made by a senior member of the team that escalation of care is appropriate and in the best interest of the patient.**

## Indications for Dialysis

- Resistant hyperkalaemia
- Diuretic resistant pulmonary oedema
- Severe acidosis
- Pericarditis, encephalopathy

## Indications for Critical Care Admission

(rather than direct admission to renal unit)

- All patients requiring CPAP/NIV/inotrope/vasopressor support
- Multi-organ failure e.g severe sepsis
- GCS<12 or fluctuating
- Severe hyperkalaemia
- Patients unable to transfer from peripheral hospitals due to lack of bed capacity who requiring urgent, life saving treatment
- BP<90 – unless known chronic hypotension *
- Fi O2 requirement >60%*

(* Will need to be discussed on a case by case basis)

Further guidance for referral and transfer of patients requiring acute RRT can be found here

# Referral proforma

**In order to prevent unnecessary delay, have the following information to hand when making a referral to either the renal or critical care team (can be printed off and filed in notes if necessary)**

| |
|---|
| **Name, age:** |
| **Summary of why a referral is being sought :** |
| **Co-morbid diseases :** |
| **Pre morbid functional status :** |
| **Recent observations (BP/Urine output/Sats/HR):** |
| **Baseline renal function:** |
| **USS result:** |
| **Urine dipstick result:** |
| **Decisions on escalation of care (if appropriate):** |
| **Date, Time:** **Signature:** |

# Special Circumstances

## AKI in Cirrhotics

The majority of AKI in cirrhotics is NOT hepatorenal syndrome. Early identification of potentially reversible factors such as volume depletion or sepsis is a vital part of managing these patients. Often the creatinine will be low (due to low muscle mass, liver dysfunction and interference with the assay by bilirubin), thus vigilance is required. Untreated AKI in this population has a particularly bad outcome

Consider causes – GI bleed/ Bacterial peritonitis/ Diuretics / Sepsis/ Intra-Abdominal Hypertension

## Rhabdomyolysis

CK levels >5000 U/L identify patients at significant risk of AKI. Mainstay of treatment is to identify causative agent (usually drugs/trauma/seizures) and to keep the patient well hydrated with IV fluids, ensuring a good urine output of approx 200ml/hr (hourly urine output measurement is essential). Forced alkaline diuresis is not performed in routine practice. If CK levels do not fall, consider ongoing exposure to drugs/ compartment syndrome/myositis as causes.

## Renal transplant patients

During episodes of intercurrent illness, transplant patients may present to their local A+E/MAU. ALL sick transplant patients should be discussed with the renal or transplant team in UHW. Most of these patients will be on immunosuppression. Certain antimicrobials such as macrolide antibiotics (clarithromycin, erythromycin), interfere with the metabolism of calcineurin inhibitors (tacrolimus, ciclosporin) and should not be routinely prescribed. The renal or transplant team should be informed prior to any adjustment to a patients immunosuppression regimen.

# Contrast Nephropathy (Inpatients)

## Risk Factors

- CKD*(eGFR<60)
- Volume depletion
- CCF
- Cirrhosis
- Myeloma

*especially diabetic nephropathy

eGFR calculator link

## Pre Contrast Administration

For patients deemed at risk, adequate hydration pre-procedure is essential. There is weak evidence supporting the use of prophylactic bicarbonate[1], normal saline is an alternative (below). Consider withholding potentially nephrotoxic drugs (page 4) for 24h pre and post procedure. Higher risk patients (e.g eGFR<30 and/or multiple risk factors) should be informed about the potential risk of contrast nephropathy.

**Prophylactic fluids**

- 1L normal saline over 12h (both pre and post procedure) **OR**
- IV Na bicarbonate **(1.26%)** 3mls/Kg/hr for 1 hour pre-procedure and 1ml/Kg/hr for 6 hours post-procedure

1).JAMA 2008; 300:1038

## Post Contrast Administration

- Ensure follow up bloods are taken **and reviewed** in patients deemed at risk.
- A significant rise in Creatinine may not be seen until 2-3 days post procedure. If patients are discharged before then, contact their primary care team to ensure that bloods are checked in the community.

**Appendix 1.3:** Publications and presentations arising from this thesis

**Publications arising from this thesis**

1. **Holmes J**, Rainer T, Geen J, Roberts G, May K, Wilson N, Williams JD, Phillips AO. Acute Kidney Injury in the era of the AKI e-alert. Clinical Journal of the American Society of Nephrology. December 2016.

2. **Holmes J**, Allen N, Roberts G, Geen J, Williams JD, Phillips AO. Acute Kidney Injury Electronic alerts in Primary Care - Findings from a large population cohort. QJM: An International Journal of Medicine. September 2017.

3. **Holmes J**, Roberts G, Geen J, Dodd A, Selby NM, Lewington A, Scholey G, Williams JD, Phillips AO. Utility of electronic AKI alerts in Intensive Care: A national multicentre cohort study. Journal of Critical Care. April 2018.

4. Gubb S, **Holmes J**, Smith G, Geen J, Williams JD, Phillips AO. Acute Kidney Injury in Children based on electronic alerts. Journal of Pediatrics. November 2019.

5. Jones A, **Holmes J**, Stephens M, Geen J, Williams JD, Donovan K, Phillips AO. Utility of electronic AKI alerts to define the epidemiology of Acute Kidney Injury in Renal Transplants. Journal of Nephrology. December 2020.

6. Phillips D, **Holmes J**, Davies R, Geen J, Williams JD, Phillips AO. The influence of socioeconomic status on presentation and outcome of acute kidney injury. QJM: An International Journal of Medicine. December 2018.

7. **Holmes J**, Phillips D, Donovan K, Geen J, Williams JD, Phillips AO. Acute Kidney Injury, Age and Socioeconomic Deprivation: Evaluation of a National data set. Kidney International Reports. March 2019.

8. **Holmes J**, Geen J, Phillips B, Williams JD, Phillips AO. Community Acquired Acute Kidney Injury: Findings from a large population cohort. QJM: An International Journal of Medicine. November 2017.

9. Phillips D, Young O, **Holmes J**, Allen LA, Roberts G, Geen J, Williams JD, Phillips AO. Seasonal pattern of incidence and outcome of Acute Kidney Injury: A National study of Welsh AKI electronic alerts. International Journal of Clinical Practice. September 2017.

10. **Holmes J**, Rainer T, Geen J, Williams JD, Phillips AO. Adding a new dimension to the weekend effect: an analysis of a national data set of electronic AKI alerts. QJM: An International Journal of Medicine. April 2018.

11. **Holmes J**, Geen J, Williams JD, Phillips AO. Recurrent Acute Kidney Injury: Predictors and impact in a large population based cohort. Nephrology Dialysis Transplantation. July 2019.

12. **Holmes J**, Roberts G, Meran S, Williams JD, Phillips AO. Understanding Electronic AKI alerts: Characterization by Definitional Rules. Kidney International Reports. May 2017.

13. **Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD, Phillips AO. The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based alert. Kidney International. August 2017.

14. **Holmes J**, Donovan K, Geen J, Williams JD, Phillips AO. Acute kidney injury demographics and outcomes: changes following introduction of electronic acute kidney injury alerts-an analysis of a national dataset. Nephrology Dialysis Transplantation. June 2020.

**Abstract presentations arising from this thesis**

**Holmes J** and May K. 'Addressing AKI in Wales: An update from the All Wales AKI Steering Group'. Platform Presentation at: Public Health Wales National Learning Event, Cardiff, UK. June 2015.

**Holmes J** and May K. 'Addressing AKI in Wales: An update from the All Wales AKI Steering Group'. Platform presentation at: Welsh Renal Clinical Network National Audit Day, Cardiff, UK. September 2015.

Phillips AO on behalf of AKI steering group. 'Addressing AKI in Wales: An update from the All Wales AKI Steering Group'. Platform presentation at: All Wales Critical Care Implementation Group Cardiff, UK, September 2015.

Phillips AO on behalf of AKI steering group. 'Acute Kidney Injury in the era of the AKI e-alert'. Platform presentation at: Wales Kidney Research Unit Annual Meeting, Cardiff, UK, UK. December 2015.

**Holmes J** on behalf of AKI steering group. 'The impact of AKI on Critical Care in Wales'. Platform Presentation at: All Wales Critical Care Implementation Group, Cardiff, UK, April 2016.

**Holmes J**, Rainer T, Geen J, Roberts G, May K, Wilson N, Williams JD, Phillips AO. 'Acute Kidney Injury in the era of the AKI e-alert'. Poster presentation at: British Renal Society/UK Renal Association Conference, Birmingham, UK. June 2016.

**Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD and Phillips AO. 'Validation of a serum creatinine based electronic (e)-alert system for Acute Kidney Injury (AKI) in a paediatric cohort'. Poster presentation at: The annual meeting of the Association for Clinical Biochemistry and Laboratory Medicine (FOCUS), Leeds, UK. June 2017.

**Holmes J**, Rainer T, Geen J, Roberts G, May K, Wilson N, Williams JD and Phillips AO. 'Acute Kidney Injury in the Era of the AKI E-Alert: A National Study'. Platform presentation at: Cwm Taf Morgannwg UHB Research and Development Conference, Cardiff, UK. November 2016.

**Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD and Phillips AO. 'Paediatric Acute Kidney Injury (AKI) identified by a change in Creatinine based electronic alert: A National Survey'. Poster presentation at: Wales Kidney Research Unit Annual Meeting, Swansea, UK. December 2016.

**Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD and Phillips AO. 'Paediatric Acute Kidney Injury (AKI) identified by a change in Creatinine based electronic alert: A National Survey'. Poster presentation at: British Renal Society/UK Renal Association, Liverpool, UK. June 2017.

**Holmes J**, Roberts G, May K, Tyerman K, Geen J, Williams JD and Phillips AO. 'Paediatric Acute Kidney Injury (AKI) identified by a change in Creatinine based electronic alert: A National Survey'. Poster presentation at: Welsh Renal Clinical Network National Audit Day, Llandrindod Wells, UK. September 2017.

Phillips AO on behalf of AKI steering group. 'AKI in Wales: An update on what information we have'. Platform presentation at: Welsh Renal Clinical Network National Audit Day, Llandrindod Wells, UK. September 2017.

**Holmes J**, Geen J, Dodd, A and Phillips AO. 'The association of Acute Kidney Injury and Social Deprivation: A National Survey'. Poster presentation at: Cwm Taf Morgannwg UHB Research and Development Conference, Cardiff, UK. November 2018.

Phillips AO on behalf of AKI steering group. 'Epidemiology and Natural History of AKI: What do electronic alerts tell us and how can we use them?'. Platform presentation at: International Society of Nephrology World Congress of Nephrology (ISN WCN), Melbourne, Australia. April 2019.

**Holmes J**, Geen J, Williams JD and Phillips AO. 'Recurrent Acute Kidney Injury: Predictors and impact in a large population based cohort'. Poster presentation at: Cwm Taf Morgannwg UHB Research and Development Conference, Cardiff, UK, November 2019.

**Holmes J**. 'Acute Kidney Injury in Paediatrics based on electronic AKI alerts'. Platform presentation at: Cwm Taf Morgannwg UHB Research and Development Conference, Cardiff, UK, November 2019.

**Appendix 3.1:** Published work 1 related to this thesis:

Holmes *et al*. (2016) 'Acute Kidney Injury in the era of the AKI e-alert', Clinical Journal of the American Society of Nephrology

# Acute Kidney Injury in the Era of the AKI E-Alert

*Jennifer Holmes,* Timothy Rainer,† John Geen,‡§ Gethin Roberts,‖ Kate May,* Nick Wilson,* John D. Williams,¶ and Aled O. Phillips,¶ on behalf of the Welsh AKI Steering Group*

## Abstract

**Background and objectives** Our aim was to use a national electronic AKI alert to define the incidence and outcome of all episodes of community– and hospital–acquired adult AKI.

**Design, setting, participants, & measurements** A prospective national cohort study was undertaken in a population of 3.06 million. Data were collected between March of 2015 and August of 2015. All patients with adult (≥18 years of age) AKI were identified to define the incidence and outcome of all episodes of community- and hospital-acquired AKI in adults. Mortality and renal outcomes were assessed at 90 days.

**Results** There was a total of 31,601 alerts representing 17,689 incident episodes, giving an incidence of AKI of 577 per 100,000 population. Community-acquired AKI accounted for 49.3% of all incident episodes, and 42% occurred in the context of preexisting CKD (Chronic Kidney Disease Epidemiology Collaboration eGFR); 90-day mortality rate was 25.6%, and 23.7% of episodes progressed to a higher AKI stage than the stage associated with the alert. AKI electronic alert stage and peak AKI stage were associated with mortality, and mortality was significantly higher for hospital-acquired AKI compared with alerts generated in a community setting. Among patients who survived to 90 days after the AKI electronic alert, those who were not hospitalized had a lower rate of renal recovery and a greater likelihood of developing an eGFR<60 ml/min per 1.73 $m^2$ for the first time, which may be indicative of development of *de novo* CKD.

**Conclusions** The reported incidence of AKI is far greater than the previously reported incidence in studies reliant on clinical identification of adult AKI or hospital coding data. Although an electronic alert system is Information Technology driven and therefore, lacks intelligence and clinical context, these data can be used to identify deficiencies in care, guide the development of appropriate intervention strategies, and provide a baseline against which the effectiveness of these interventions may be measured.

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## Introduction

The reported incidence of AKI varies depending on its definition, the clinical setting in which it is detected, and the population studied. The definitions of AKI used in many previous studies in the literature varied, making direct comparison of these difficult. In 2009, the National Confidential Inquiry into Patient Outcome and Death (1) report identified significant deficiencies in the management of AKI in hospitals in the United Kingdom. This led to the development and implementation of strategies, such as the use of electronic results reporting to aid early AKI recognition (2). In response, the Royal College of Physicians, at a consensus conference in the United Kingdom, recommended the adoption of an electronic alert (e-alert) system to aid in the early identification of AKI (3). On the basis of a presumption that early identification may help raise standards of care and improve patient outcomes, an automated real–time e-alert system for AKI on the basis of the Kidney Disease Improving Global Outcomes (KDIGO) change in creatinine diagnostic criteria has been established and implemented nationally across all areas of the National Health Service in Wales. Using a centralized system of data collection, the aim of this study was to provide a comprehensive characterization of the base incidence and the definition of AKI identified by e-alerts (AKI) and its outcome across both primary and secondary care.

## Materials and Methods

### Setting

The National Health Service in Wales, which serves a population of 3.06 million, is organized into seven local health boards (LHBs) (Supplemental Figure 1). Data were collected from all health boards. The study was approved under Service Evaluation Project Registration.

### Development of the Electronic Reporting System

The all Wales Laboratory Information Management System (InterSystems TrakCare Lab) in real time automatically compares measured creatinine values on an individual patient with previous results to generate alerts (Supplemental Figure 2) on the basis of the KDIGO AKI criteria (Supplemental Table 1).

The definition of AKI, therefore, relies on creatinine but does not rely on urine output. A summary of the rules is shown in Supplemental Table 2, and each e-alert code together with the comment that accompanies the e-alert are shown in Supplemental Table 3. Any patient presenting with AKI but without a measurement of renal function in the previous 365 days will, therefore, not be included in the study.

### Data Collection

Prospective data were collected for all patients with adult (≥18 years of age) AKI in Wales between March of 2015 and August of 2015. Clinical location, 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. An incident AKI episode was defined as 90 days (*i.e.*, any AKI e-alert for the same patient within 90 days); the incident alert was not considered a new episode. Peak AKI stage was assigned by comparing the highest serum creatinine (SCr) value during an AKI incident episode with the baseline SCr of the incident alert. To prevent inclusion of patients known to be receiving RRT, alerts transmitted by patients from a renal, renal transplant, or dialysis setting and those by patients who had a previous blood test in a dialysis setting were excluded. All incident patients with AKI alerted for the first time in a nonrenal location before transfer to the regional renal unit.

Incidence rate was calculated using Mid-2013 Office for National Statistics (ONS) Population Estimates. Patients for whom the first e-alert was generated from a creatinine value measured in primary care were classified as primary care AKI. All patients for whom the first alert was issued during a hospital admission and who also had a normal SCr value generated in a hospital setting within the preceding 7 days were defined as patients with hospital-acquired AKI (HA-AKI). Patients alerting in a noninpatient setting (including accident and emergency/acute assessment units) and not alerting in primary care were classified as patients with nonprimary care community–acquired AKI (CA-AKI). Primary care and nonprimary care CA-AKI, therefore, collectively represent CA-AKI.

Hospitalization of CA-AKI was defined as first or second measurement of renal function in an inpatient setting (within 7 days) after the alert. Mortality data were collected from the Welsh Demographic Service. Patients were censored at 1 year for survival analysis. Renal outcome analysis required patients to have 90-day follow-up data available and included only those patients surviving at this time point. Linear regression analysis of renal outcome included surviving and nonsurviving patients. Nonrecovery from an AKI episode was defined as achievement of an SCr value closest to and within 90 days, still consistent with the definition of AKI compared with baseline SCr values. Preexisting CKD was defined as an eGFR (calculated by the Chronic Kidney Disease Epidemiology Collaboration eGFR equation [4]) <60 ml/min per 1.73 $m^2$ derived from the baseline SCr. A worsening eGFR was calculated using the eGFR value closest to and within 90 days and defined by a decline from baseline eGFR of >15% or >5 ml/min per 1.73 $m^2$ (5).

The Welsh Index of Multiple Deprivation (WIMD) is the Welsh Government official measure of relative deprivation. This generates a rank (WIMD score) for 1909 lower superoutput geographic areas (LSOAs) in Wales on the basis of eight domains; income, employment, health, education, access to services, community safety, physical environment, and housing (6). Patients were georeferenced to an LSOA of residence and ranked according to WIMD score. Ranked data were categorized into percentiles, with percentile 1 the most deprived and percentile 100 the least deprived. Patients were aggregated to their geographic area (LSOA of residence), and incidence of AKI was calculated using the total adult population in each LSOA derived from Mid-2013 ONS Population Estimates.

Statistical analysis was carried out using SPSS software, version 20 (IBM SPSS, Chicago, I ); *t* test was used for analysis of normally distributed data. Categorical data were compared using a Pearson chi–squared test. Multivariate Cox proportional hazard modeling was used to analyze patient survival. *P* values <0.05 were considered statistically significant.

### Validation

The diagnostic accuracy was determined by manually checking baseline creatinine values for a sample of 200 patients distributed across each rule and e-alert code and across two LHBs. All of the e-alerts generated conformed to the mathematic definition of AKI.

When patients known to be on dialysis were not identified as such by the request through the location code, a proportion of patients known to be on dialysis generated an AKI e-alert. This was only applicable to ABS1, ABS2, and DELTA1 codes (Supplemental Table 3). For ABS1 codes, 89% of flagged patients were known to be on dialysis. In total, 105 patients were flagged by this code. These were all excluded from the analysis, and therefore, 11% of the cohort identified by this code (12 patients) with probable AKI were excluded from the overall analysis. For ABS2 code, 26% of patients were patients known to be on dialysis. ABS2 accounted for a total of 562 patients. These have been included in the analysis, and therefore, by extrapolation, 146 patients likely to be on dialysis are included in the analysis. For the DELTA1 code, 60% of those flagged who had a creatinine of >4.5 mg/dl were patients on dialysis. In total, 89 patients were flagged by this code and had a creatinine of >4.5 mg/dl. These were excluded, and therefore, 40% of the cohort identified by this code (36 patients) with probable AKI were excluded. Using these criteria results in a false negative rate of 0.27% (exclusion of patients with AKI) and a false positive rate of 0.83% (inclusion of patients known to be on dialysis).

## Results

### Incidence and Demographics

We observed a total of 31,601 alerts (Table 1). The majority (62.9%) of patients generated only one alert. Of those patients who triggered multiple e-alerts, 18.5% generated two alerts, 8.3% generated three alerts, 4.2% generated four alerts, 2.1% generated five alerts, and 1.3% generated six alerts, with the remainder generating between seven and 27 alerts. Only 2.8% of incident episodes were the result of a second episode from the same patient.

**Table 1. Incidence/demography of AKI**

| Variable | All AKI | | | |
|---|---|---|---|---|
| *n* Per 100,000 population (*n*) | 577 (17,689) | | | |
| **AKI severity, % (*n*)** | | | | |
| Stage 1 | 78.7 (13,922) | | | |
| Stage 2 | 14.3 (2522) | | | |
| Stage 3 | 7.0 (1245) | | | |
| **AKI rule, % (*n*)** | | | | |
| Rule 1 | 9.9 (1753) | | | |
| Rule 2 | 27.1 (4799) | | | |
| Rule 3 | 63.0 (11,137) | | | |
| **Clinical location, % (*n*)** | | | | |
| Hospital | 41.2 (7288) | | | |
| Community | 49.3 (8724) | | | |
| | All AKI | HA-AKI | CA-AKI | |
| **Health board, *n* per 100,000 population (*n*)** | | | | |
| Abertawe Bro Morgannwg UHB | 549 (2857) | 396.9 | 216.6 | |
| Aneurin Bevan UHB | 550 (3185) | 189.9 | 265.9 | |
| Betsi Cadwaladr UHB | 564 (3906) | 219.1 | 282.2 | |
| Cardiff and Vale UHB | 513 (2457) | 247.7 | 239.1 | |
| Cwm Taf UHB | 814 (2402) | 313.8 | 429.0 | |
| Hywel Dda UHB | 693 (2659) | 258.4 | 392.5 | |
| Powys THB | 60 (80) | 5.3 | 46.0 | |
| | All AKI | AKI Stage 1 | AKI Stage 2 | AKI Stage 3 |
| Mean age±SD, yr | 71.1±17.0 | 71.0±17.3 | 71.8±15.9 | 70.5±15.9 |
| **Sex, % (*n*)** | | | | |
| Men | 46.9 (8285) | 46.1 (6407) | 46.4 (1171) | 56.8 (707) |
| Women | 53.1 (9388) | 53.9 (7499) | 53.6 (1351) | 43.2 (538) |
| Preexisting CKD, % (*n*) | 41.9 (6877) | 38.5 (5354) | 34.5 (870) | 52.5 (653) |
| Mean baseline SCr, mg/dl | 1.0 | 1.0 | 0.9 | 1.4 |
| Mean baseline eGFR, ml/min per 1.73 $m^2$ | 71.6 | 72.0 | 74.4 | 61.7 |
| Mean alert SCr, mg/dl | 1.8 | 1.5 | 2.1 | 4.7 |
| Mean peak SCr, mg/dl | 2.3 | 1.9 | 2.5 | 5.3 |

Data on patient sex were missing for 16 patients and excluded from analysis of the sex variable. Baseline eGFR data were missing for 24 patients and excluded from analysis of the preexisting CKD variable. HA-AKI, hospital-acquired AKI; CA-AKI, community-acquired AKI; UHB, University Health Board; THB, Teaching Health Board; SCr, serum creatinine.

The alerts generated represent 17,689 episodes of AKI. This translates into an incidence of AKI of 577 per 100,000 population over the 6-month timeframe and 1.2 patients per 100 person-years. The majority (78.7%) of episodes were classified as AKI stage 1 at presentation, with 14.3% classified as AKI stage 2 and 7.0% classified as AKI stage 3; 23.7% of stages 1 and 2 episodes progressed to a higher peak AKI stage relative to the incident AKI alert stage: 15.1% (944) and 9.0% (562) of AKI stage 1 progressed to AKI stages 2 and 3, respectively, and 21.8% (247) of AKI stage 2 progressed to AKI stage 3.

### CA-AKI and HA-AKI

The distribution of e-alerts by the location in which the alert was generated is shown in Figure 1A. CA-AKI and HA-AKI accounted for 49.3% and 41.2% of all alerts, respectively. The remaining 9.5% of alerts were generated in an inpatient setting, but because no results were available for the previous 7 days, it was not possible to confidently classify these as either CA-AKI or HA-AKI. For both AKI in the community and that acquired in hospital, the overwhelming majority was AKI stage 1.

The distribution of clinical locations for both nonprimary care CA-AKI and HA-AKI alerts, stratified by AKI stage, is shown in Figure 1, B and C (Supplemental Tables 4 and 5). The majority (53%) of AKI acquired in a nonprimary care community setting is first detected in the accident and emergency department. For HA-AKI, the largest single cohort is acquired in a general medical inpatient setting (25%) followed closely by the combination of general surgical and trauma/orthopedics, which accounts for 24% of all HA-AKI.

For incident CA-AKI episodes, 30.6% were generated by an alert issued to primary care, which represents 14.6% of all of the incident AKI episodes. The remainder of CA-AKI was accounted for by patients alerting in a noninpatient setting (including accident and emergency/acute assessment units) but excluding primary care. Primary care AKI

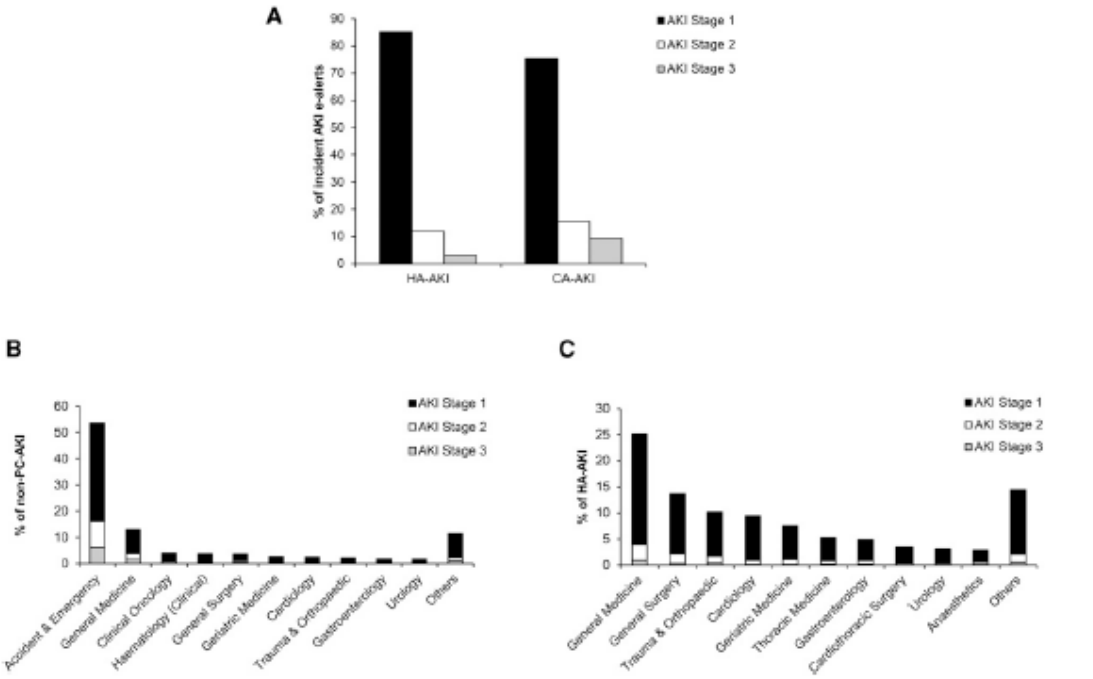


**Figure 1. | Source of incident AKI electronic alerts (e-alerts).** (A) Distribution of AKI stages for hospital-acquired AKI (HA-AKI) and community-acquired AKI (CA-AKI). (B) Percentage and number of nonprimary care (non-PC) patients with CA-AKI divided according to clinical specialty and AKI stage. Clinical specialty data were missing for 289 patients and excluded from analysis. (C) Percentage and number of patients with HA-AKI divided according to clinical specialty and AKI stage. Clinical specialty data were missing for 692 patients and excluded from analysis.

e-alerts were followed by hospital admission in 31% of patients (Figure 2A). For primary care CA-AKI, admission was associated with greater severity of renal injury, with 26% of patients with AKI stage 1 admitted compared with 42% of patients with AKI stage 2 and 56% of patients with AKI stage 3. Nonprimary care community AKI e-alerts were followed by hospital admission in 71% of patients (Figure 2B). For this group, admission to hospital was not related to AKI severity.

There was a positive relationship between the time to repeat measurement of renal function and hospitalization, with significantly longer mean times for patients not hospitalized for primary care CA-AKI (7.4±13.8 versus 11.9±14.1 days; $P<0.001$) and nonprimary care CA-AKI (2.7±7.6 versus 11.1±16.2 days; $P<0.001$). In nonhospitalized CA-AKI at the time of retesting, 18.2% of patients had additional elevation of SCr (compared with 40.9% of patients with CA-AKI who were hospitalized). Of those patients with CA-AKI not diagnosed in primary care, 19.9% of patients had a measurement of SCr (that did not generate an e-alert) in the preceding 30 days.

### Regional Variations

The geographic variation of AKI incidence is shown in Table 1. The low overall incidence in Powys and the higher incidence in Hywel Dda likely reflect the organization of health care, with no secondary care services in Powys. Its population is served predominantly by hospital services in the neighboring Hywel Dda Health Board (a smaller proportion may access hospital service in English hospitals, for which we have no data). The high incidence in Cwm Taf occurs in both hospital– and community–acquired groups. This board serves the most socially deprived population in the principality. The relationship between incidence of AKI and patient socioeconomic status is shown in Figure 3. There was a strong negative correlation between ranking by WIMD score and the incidence of AKI ($r=-0.91$; 95% confidence interval [95% CI], −0.94 to −0.87; $P<0.001$).

### Significance of an Episode of AKI

**Mortality.** Ninety-day mortality for AKI is shown in Figure 4. Overall 90-day mortality was 25.6%. Mortality was significantly higher ($P<0.001$) in HA-AKI compared with CA-AKI (Figure 4A). For CA-AKI, mortality (Figure 4, B and C) was significantly higher in the hospitalized cohort ($P<0.001$) and nonprimary care CA-AKI ($P<0.001$). Cox regression proportional hazard modeling analysis (with follow-up data up to and including 12 months) showed higher hazards of death associated with older age (hazard ratio [HR], 1.03; 95% CI, 1.03 to 1.03), more severe AKI at presentation (AKI stage 2/3 versus AKI stage 1; HR, 1.43; 95% CI, 1.34 to 1.54), and peak AKI stage (AKI stage 2/3 versus AKI stage 1; HR, 2.36; 95% CI, 2.20 to 2.53). Increased hazards of death were associated with nonprimary care CA-AKI (unadjusted HR, 1.77; 95% CI, 1.59 to 1.97; adjusted HR, 1.65; 95% CI, 1.48 to 1.84; $P<0.001$) and HA-AKI (unadjusted HR, 2.04; 95% CI, 1.83 to 2.26; adjusted HR, 1.98; 95% CI, 1.78 to 2.19; $P<0.001$) compared with

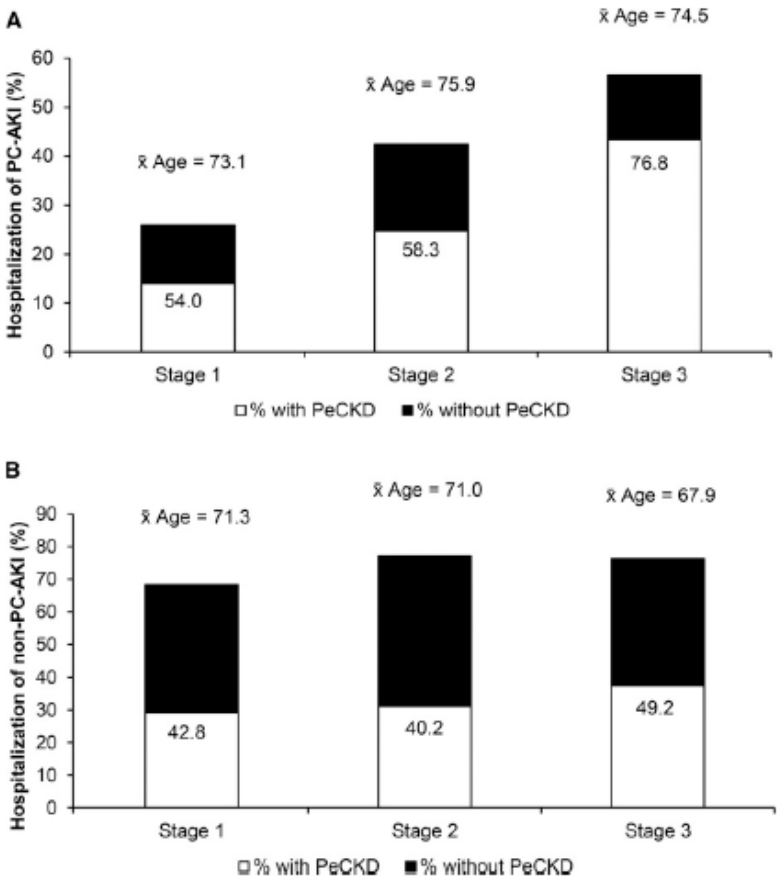


**Figure 2. | Differing hospitalization rates for community-acquired AKI subsets.** (A) Percentage, average age, and percentage with preexisting CKD (shaded area of each bar) in patients with primary care AKI (PC-AKI) who were hospitalized divided according to AKI stage (total number of patients: stage 1, 1531; stage 2, 255; and stage 3, 175). (B) Percentage, average age, and percentage with preexisting CKD (shaded area of each bar) in patients with nonprimary care AKI (non–PC-AKI) who were hospitalized divided according to AKI stage (total number of patients: stage 1, 3727; stage 2, 889; stage 3, and 542). PeCKD, preexisting CKD.

primary care CA-AKI. For CA-AKI, hospitalization was also associated with increased hazard of death (HR, 1.31; 95% CI, 1.23 to 1.39; $P<0.001$).

**Renal Outcomes.** The relationship between the incident AKI e-alert and subsequent renal function is shown in Figure 5. Significantly more patients did not recover their renal function after an episode of HA-AKI compared with CA-AKI (14.6% versus 7.9%; $P<0.001$). In contrast, more patients with CA-AKI and preexisting CKD were likely to have worsening renal function after the AKI episode than after HA-AKI (42.5% versus 35.9%; $P=0.002$). For the whole cohort, more severe AKI at presentation (AKI stage 2/3 versus AKI stage 1; HR, 1.82; 95% CI, 1.64 to 2.03) and peak AKI stage (AKI stage 2/3 versus AKI stage 1; HR, 3.98; 95% CI, 3.49 to 4.54) were associated with nonrecovery of renal function.

For CA-AKI picked up in primary care (Figure 5B), nonrecovery of renal function was significantly higher than in nonprimary care CA-AKI ($P<0.001$). Similarly, AKI detected in primary care was associated with a greater likelihood of developing eGFR<60 ml/min per 1.73 $m^2$ for the first time ($P<0.001$), and of those patients with preexisting CKD, patients with primary care CA-AKI were significantly more likely to experience a worsening eGFR ($P<0.001$). The relationship between admission to hospital and renal outcome for all CA-AKI groups is shown in Figure 5C. Hospitalization was associated with better outcome in terms of recovery from the acute episode ($P<0.001$), a lower proportion of patients developing an eGFR<60 ml/min per 1.73 $m^2$ for the first time, and fewer patients with preexisting CKD experiencing worsening eGFR ($P<0.001$ for both parameters). By linear regression, better acute outcome adjusted for both incident and peak AKI stages was also associated with hospitalization (HR, 1.23; 95% CI, 1.16 to 1.29; $P<0.001$).

## Discussion

The majority of publications of large series characterizing AKI rely on making and recording an accurate diagnosis of AKI through hospital coding or retrospective review of hospital records (7–10). Although providing

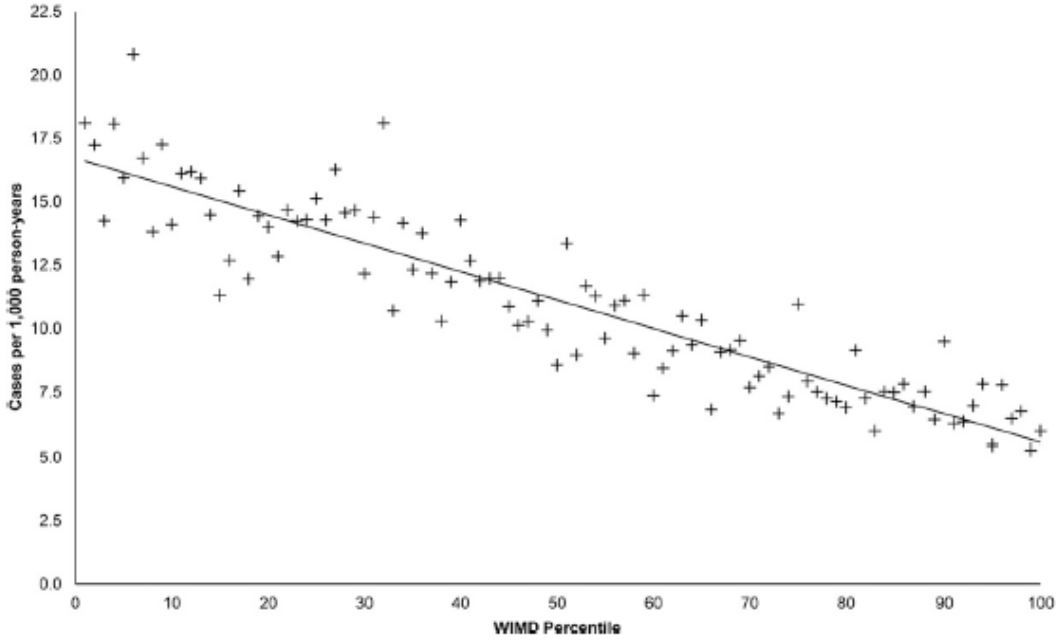


**Figure 3. | Negative association between incidence of AKI and the index of social deprivation.** Two hundred twenty-one patients with missing postcode data were excluded from analysis; 121 patients with English postcodes were excluded from analysis. WIMD, Welsh Index of Multiple Deprivation, where percentile 1 is the most deprived and percentile 100 is the least deprived.

essential information on the epidemiology of AKI, there is significant potential for AKI episodes to be missed, resulting in underestimation of the true incidence of AKI. There are publications that have sought to overcome this *via* a biochemical identification of AKI as a trigger to identify the patients. These are, however, either single–center, hospital–based studies (11,12) or reliant on an e-alert that was not on the basis of an internationally agreed on AKI definition (13). To address this, we used a national dataset to provide a comprehensive characterization of the incidence of electronic AKI alerts and the subsequent clinical course.

The first key finding in this study is the high incidence of AKI. Previous studies have suggested an annual incidence of 200–300 per 100,000 in high-income countries (14). The use of an alert-based system for patient identification, therefore, overcomes systematic under-reporting of AKI associated with previous studies. The study also shows a significant association of AKI with renal function at 90 days after the incident episode. For the whole cohort of >17,000 patients, more than one quarter of the population either developed an eGFR<60 ml/min per 1.73 $m^2$ for the first time, which may be indicative of the development of *de novo* CKD, or experienced worsening of preexisting CKD after the incident AKI e-alert, which may affect the need to plan for long-term provision of RRT.

In contrast to studies describing HA-AKI, less is known regarding the characterization of CA-AKI. Published studies are mainly reliant on small patient numbers and because of geographic differences in disease patterns, may not be directly applicable to all populations (15–17). The findings in this manuscript are, however, consistent with our previous publications (5,18) and other recent smaller studies from Scotland (19) and Kentucky (20) showing that CA-AKI represents a significant proportion of all AKI. The outcome for CA-AKI defined by an e-alert is better than that for HA-AKI. This needs to be qualified by the observation that a significant proportion of patients with CA-AKI is not admitted to hospital and therefore, is not reported on in the majority of publications that characterize the nature and outcome of CA-AKI.

In this study, there is significant mortality after an AKI e-alert. Mortality is clearly higher in the cohort of patients admitted to the hospital; however, it is of note that, even in patients with CA-AKI who are not admitted to hospital, there is a 90-day mortality of 10%–15%, suggesting that, even in this group for which admission may not be appropriate or desirable, AKI is a marker of frailty. In the surviving patients, it is also of note that nonadmission is associated with a significantly worse renal outcome. Although in some patients, nonadmission may be appropriate and reflect a conscious decision (*e.g.*, in the setting of palliative care), our previous published data (5,18) and the data on time to repeat measurement of renal function in this study suggest that nonadmission is, at least in part, because of lack of recognition of the significance of the alert. Our data are, however, consistent with the recent report by Sawhney *et al.* (21), in which patients with nonadmitted AKI, while having a lower mortality, were associated with greater nonrecovery of renal function.

On a national level, our data suggest regional variations in the incidence of AKI, with two areas in particular highlighted as outliers. The very small incidence in Powys likely reflects the rural nature of the area, with the

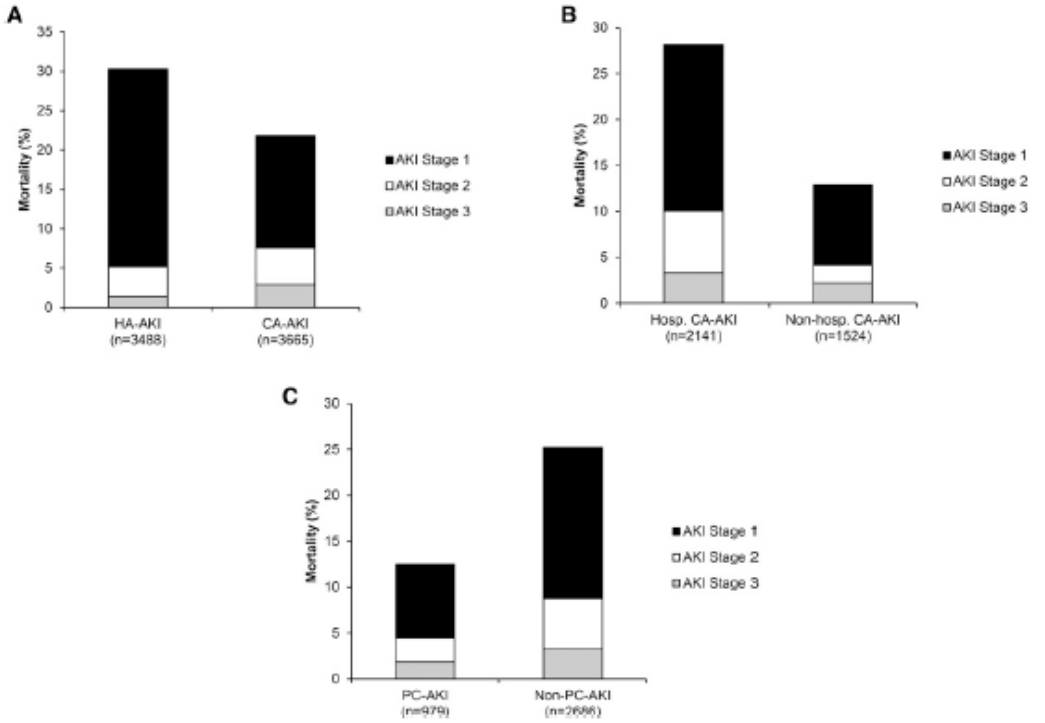


**Figure 4. | Differing ninety-day mortality rates associated with incident AKI electronic alerts for clinical location of AKI subsets.** (A) Percentage of patients with AKI who died divided according to place of identification of AKI. (B) Percentage of patients with community-acquired AKI (CA-AKI) who died divided according to hospitalization. (C) Percentage of patients with CA-AKI who died divided according to place of identification of AKI. Mortality was significantly higher for all of the admitted groups ($P<0.001$ compared with nonadmitted groups). Mortality rates were comparable in the admitted nonprimary care CA-AKI and hospital-acquired AKI (HA-AKI) groups, which were significantly higher than in the primary care AKI (PC-AKI) admitted cohort ($P<0.01$). Numbers of patients with data available are indicated in parentheses on the *x* axis. Shading indicates the proportion of patients who died by AKI stage. Hosp. CA-AKI, hospitalized community–acquired AKI; non-hosp. CA-AKI, nonhospitalized community–acquired AKI; non–PC-AKI, nonprimary care AKI.

population relying on hospitals in neighboring areas. Even accepting this discrepancy, the reported incidence is very low. Access to hospital facilities and renal services has long been established as a factor influencing the reported incidence of CKD (22,23), and it is interesting to speculate that the same may be true in terms of awareness of AKI. The second notable exception in AKI incidence is Cwm Taf. The WIMD (6) is produced at a small area level called LSOA and derived from a broad range of factors; 73 of the 188 LSOAs in this LHB (39%) are among the most deprived one fifth in Wales. The tight association of AKI incidence and WIMD rank across the whole cohort supports the notion that a higher prevalence of AKI is associated with social deprivation, which has been previously described for CKD (24,25). Although beyond the scope of this study, we speculate that this, at least in part, reflects a higher incidence of comorbidities, which are AKI risk factors (26), in areas of social deprivation.

Although this study is, to our knowledge, the first national study using an e-alert–based system to characterize the magnitude and effect of AKI, its findings need to be qualified by its limitations. Because the e-alert system is Information Technology driven, it lacks intelligence, and therefore, there is no clinical context applied. For this reason, the variation in SCr seen in patients on dialysis, unless specifically flagged by location, leads to a number of false positives. To minimize this effect, we have excluded incident patients flagged by two codes (ABS1 and DELTA1), which also excluded some patients with true AKI. The study is also limited in that any patient presenting with AKI but without a measurement of renal function in the previous 365 days will not be included. Using an Information Technology-based approach also precludes inclusion of clinical information, such as patient comorbidity and linkage to primary care datasets, and lacks the details of the cause of AKI, the need for RRT, and the cause of death. It should also be noted that the data collected are for a 6-month period, and therefore, potential seasonal effects on incidence may be lost. Although we have collected data on the development of CKD, this is limited by outcome data to 90 days only, and therefore, longer-term studies of follow-up are needed to truly describe the association with progressive CKD. It should also be noted that the outcomes reported in our study may be influenced by the transmission of the alert, making direct comparison with other studies difficult. Despite these limitations, our

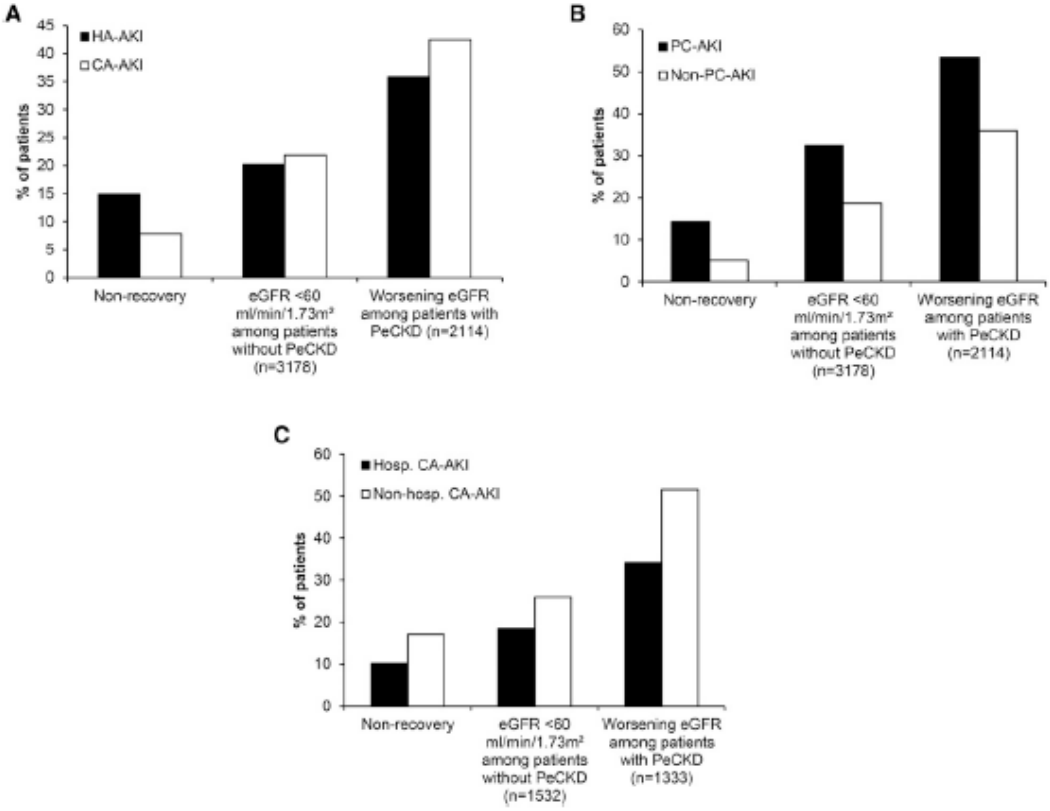


**Figure 5. | Differing renal outcomes associated with AKI electronic alerts for clinical location of AKI subsets.** (A) Renal outcome of patients with AKI divided according to place of identification of AKI. Of the patients for whom 90-day follow-up data were available, 1841 (1047, hospital-acquired AKI [HA-AKI]; 794, community-acquired AKI [CA-AKI]) had died within the 90-day follow-up period and were excluded from analysis. (B) Renal outcome of patients with CA-AKI divided according to place of identification of AKI. Of the patients for whom 90-day follow-up data were available, 794 (121, primary care–acquired AKI [PC-AKI]; 673, nonprimary care–acquired AKI [non–PC-AKI]) had died within the 90-day follow-up period and were excluded from analysis. Nonrecovery is expressed as a percentage of the whole cohort and was defined as achievement of a serum creatinine (SCr) value closest to and within 90 days still consistent with the definition of AKI in comparisons to baseline SCr values. (C) Renal outcome of patients with CA-AKI divided according to hospitalization. Of the patients for whom 90-day follow-up data were available, 794 (599, hospitalized community–acquired AKI [Hosp. CA-AKI]; 195, nonhospitalized community–acquired AKI [Non-hosp. CA-AKI]) had died within the 90-day follow-up period and were excluded from analysis.

study provides the first large–scale description of AKI using a creatinine–based electronic AKI alert.

**Acknowledgments**

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**Disclosures**

None.

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**Title:** *Acute Kidney Injury in the era of the AKI e-alert*

**Supplemental Material**

**Supplemental Table 1.** Staging of AKI

**Supplemental Table 2.** E-alert rules.

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

**Supplemental Table 4.** Specialties labelled 'Other' in Figure 1C

**Supplemental Table 5.** Specialties labelled 'Other' in Fig 1D

**Supplemental Figure 1:** Geographical location of Welsh Local Health boards and their associated descriptive demographic data.

**Supplemental Figure 2:** Algorithm for generating e-alerts for Acute Kidney Injury based on serum creatinine (SCr) changes with time.

**Supplemental 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 |

**Supplemental 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* |

**Supplemental 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.

**Supplemental Table 4.** Specialties labelled 'Other' in Figure 1C

| Specialty | N AKI episodes | % |
|---|---|---|
| Thoracic Medicine | 85 | 1.45% |
| Medical Oncology | 82 | 1.40% |
| Rheumatology | 65 | 1.11% |
| Nephrology | 54 | 0.92% |
| Endocrinology | 45 | 0.77% |
| GP Other | 30 | 0.51% |
| Cardiothoracic Surgery | 29 | 0.50% |
| Rehabilitation | 27 | 0.46% |
| Gynaecology | 25 | 0.43% |
| Chemical Pathology | 25 | 0.43% |
| Clinical Pharmacology and therapeutics | 24 | 0.41% |
| Anaesthetics | 17 | 0.29% |
| Palliative Medicine | 15 | 0.26% |
| Pain Management | 14 | 0.24% |
| Old Age Psychiatry | 14 | 0.24% |
| Obstetrics (for patients using a bed) | 13 | 0.22% |
| Dermatology | 13 | 0.22% |
| Mental Illness | 12 | 0.21% |
| ENT | 10 | 0.17% |
| Paediatrics | 9 | 0.15% |
| Ophthalmology | 6 | 0.10% |
| Neurology | 6 | 0.10% |
| Plastic Surgery | 6 | 0.10% |
| Oral Surgery | 5 | 0.09% |
| Not Known | 5 | 0.09% |
| Obstetrics PN (outpatients) | 4 | 0.07% |
| Haematology (non-clinical) | 4 | 0.07% |
| Arts therapist | 4 | 0.07% |
| Radiology | 4 | 0.07% |
| Obstetrics AN (outpatients) | 3 | 0.05% |
| Mental Handicap | 2 | 0.03% |
| Community Medicine | 2 | 0.03% |
| Genito Urinary Medicine | 2 | 0.03% |
| Clinical Immunology and Allergy | 2 | 0.03% |
| Midwifery | 1 | 0.02% |
| General Pathology | 1 | 0.02% |
| Restorative Dentistry | 1 | 0.02% |

**Supplemental Table 5.** Specialties labelled 'Other' in Fig 1D

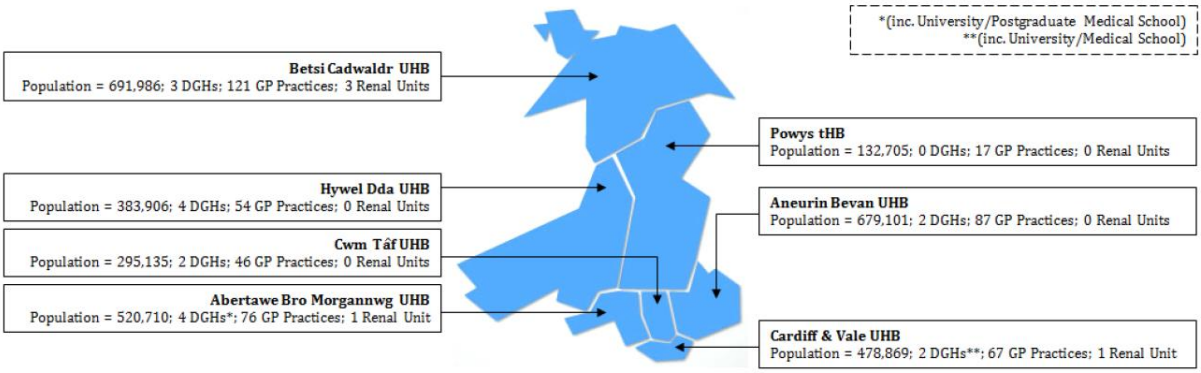
| Specialty | N of AKI episodes | % |
|---|---|---|
| Haematology (Clinical) | 135 | 2.05% |
| Endocrinology | 117 | 1.77% |
| Rehabilitation | 95 | 1.44% |
| Obstetrics (for patients using a bed) | 81 | 1.23% |
| Gynaecology | 79 | 1.20% |
| Accident & Emergency | 62 | 0.94% |
| Old Age Psychiatry | 59 | 0.89% |
| Nephrology | 59 | 0.89% |
| GP Other | 50 | 0.76% |
| Clinical Oncology | 47 | 0.71% |
| Neurosurgery | 27 | 0.41% |
| Mental Illness | 23 | 0.35% |
| Clinical Pharmacology and therapeutics | 17 | 0.26% |
| ENT | 16 | 0.24% |
| Paediatrics | 15 | 0.23% |
| Medical Oncology | 12 | 0.18% |
| Neurology | 9 | 0.14% |
| Oral Surgery | 7 | 0.11% |
| Plastic Surgery | 7 | 0.11% |
| Community Medicine | 6 | 0.09% |
| Rheumatology | 4 | 0.06% |
| Dermatology | 4 | 0.06% |
| Chemical Pathology | 3 | 0.05% |
| Clinical Genetics | 3 | 0.05% |
| Ophthalmology | 2 | 0.03% |
| General Pathology | 2 | 0.03% |
| Midwifery | 2 | 0.03% |
| Restorative Dentistry | 1 | 0.02% |
| Genito Urinary Medicine | 1 | 0.02% |
| Psychotherapy | 1 | 0.02% |
| Radiology | 1 | 0.02% |
| Palliative Medicine | 1 | 0.02% |
| Obstetrics AN (outpatients) | 1 | 0.02% |
| Pain Management | 1 | 0.02% |
| Mental Handicap | 1 | 0.02% |

**Supplemental Figure Legends:**

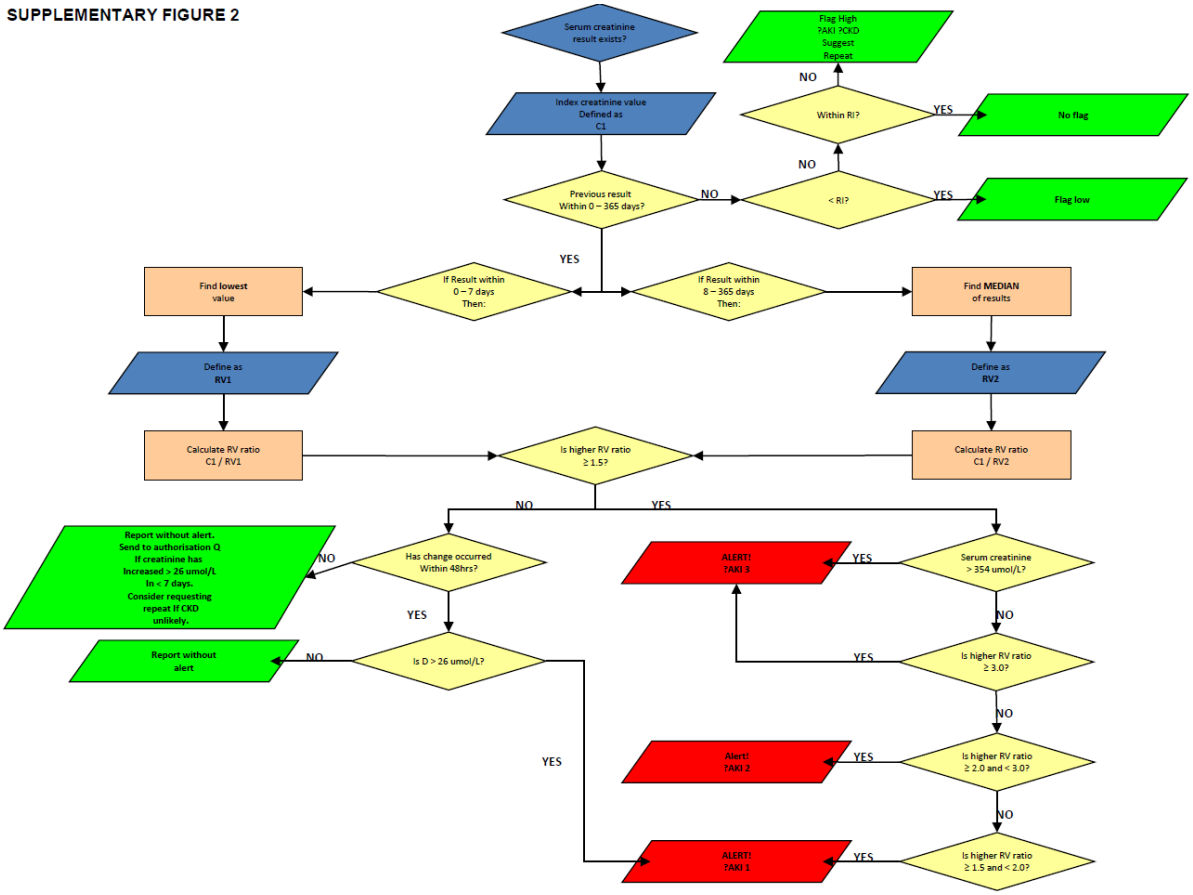
**Supplemental Figure 1:** Geographical location of Welsh Local Health boards and their associated descriptive demographic data. UHB, University Health Board; tHB, Teaching Health Board; DGH, District General Hospital; GP, General Practitioner.

**Supplemental Figure 2:** 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.

**SUPPLEMENTARY FIGURE 1**




**SUPPLEMENTARY FIGURE 2**



**Appendix 3.2:** Published work 2 related to this thesis:

Holmes *et al*. (2017) 'Acute kidney injury electronic alerts in primary care - findings from a large population cohort', QJM: An International Journal of Medicine

QJM: An International Journal of Medicine, 2017, 577–582

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Original paper

ORIGINAL PAPER

# Acute kidney injury electronic alerts in primary care - findings from a large population cohort

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## Summary

**Background:** Electronic reporting of AKI has been used to aid early AKI recognition although its relevance to CA-AKI and primary care has not been described.
**Aims:** We described the characteristics and clinical outcomes of patients with CA-AKI, and AKI identified in primary care (PC-AKI) through AKI e-Alerts.
**Design:** A prospective national cohort study was undertaken to collect data on all e-alerts representing adult CA-AKI.
**Method:** The study utilized the biochemistry based AKI electronic (e)-alert system that is established across the Welsh National Health Service.
**Results:** 28.8% of the 22 723 CA-AKI e-alerts were classified as PC-AKI. Ninety-day mortality was 24.0% and lower for PC-AKI vs. non-primary care (non-PC) CA-AKI. Hospitalization was 22.3% for PC-AKI and associated with greater disease severity, higher mortality, but better renal outcomes (non-recovery: 18.1% vs. 21.6%; progression of pre-existing CKD: 40.5% vs. 58.3%). 49.1% of PC-AKI had a repeat test within 7 days, 42.5% between 7 and 90 days, and 8.4% was not repeated within 90 days. There was significantly more non-recovery (24.0% vs. 17.9%) and progression of pre-existing CKD (63.3% vs. 47.0%) in patients with late repeated measurement of renal function compared to those with early repeated measurement of renal function.
**Conclusion:** The data demonstrate the clinical utility of AKI e-alerts in primary care. We recommend that a clinical review, or referral together with a repeat measurement of renal function within 7 days should be considered an appropriate response to AKI e-alerts in primary care.

## Introduction

It is well established that AKI requiring renal replacement therapy is associated with a high rate of in-hospital mortality.[1] Less severe degrees of renal injury, have also been associated with increased mortality, prolonged in-patient hospital stay and increased costs.[2,3] In addition, AKI has long-lasting detrimental

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effects on a patient's health, with an increased incidence of subsequent Chronic Kidney Disease (CKD) and higher mortality.[4–7] 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 (e)-alert system for AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) 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.[8] Agreed criteria to define AKI are based on changes in creatinine which are presumed to have occurred within the preceding 7 days.[9] Many patients, especially in primary care, will have no test results within a week. The AKI e-alert therefore utilizes a pragmatic adaptation of this definition using three different look-back periods to compare creatinine results.[10]

In contrasts to studies of AKI in hospitalized patients,[7,11–16] little data is available on the patterns of community acquired AKI, AKI in primary care and AKI which may not be associated with hospitalization.[17–21] As a result, there remains limited research focused on the role of general practice in prevention and management of AKI. Recent data however, suggest clinical outcomes in patients with acute elevations of serum creatinine in primary care, who are not admitted to hospital are significantly worse than those with stable kidney function.[22] To highlight AKI in the community, electronic AKI alerts are currently being issued to Primary Care in the UK. The aim is to encourage early clinical assessment of acute illness and volume status, prompt review of medications with temporary cessation of nephrotoxic medications where appropriate. Although electronic reporting of AKI has been advocated, its relevance to CA-AKI and primary care has not been described. Consequently, there is no specific guidance on the appropriate response to an AKI e-alert in this setting.

## Materials and methods

### Setting

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

### Development of electronic reporting system

The previously described (and validated) Welsh electronic AKI reporting system[23] utilizes the all Wales Laboratory Information Management System (LIMS), (InterSystems TrakCare Lab) which in real time automatically compares measured serum creatinine (SCr) values on an individual patient against previous results, to generate alerts using an algorithm based on changes in SCr level and KDIGO AKI staging criteria (Supplementary Figure 1). Three 'rules' are applied to generate alerts differing in the time period from which the baseline creatinine is obtained. Rule 1 alerts represent a >26 μmol/l increase in SCr within the previous 48h 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 8–365 days. Creatinine is measured using kinetic Jaffe methodology on various analytical platforms across Wales.

### Data collection

Prospective data was collected for all cases of adult (≥18 years of age) community acquired (CA)-AKI in Wales between November 2013 and April 2016. We defined an incident episode of AKI as 90 days, i.e. any AKI e-alert for the same patient within 90 days of a previous alert was not considered a new episode. The Medical Record Number (MRN) was used as the patient identifier. This is an unique reference number allocated to each patient registered in the National Laboratory Information Management System (LIMS) and allows for multiple visits/blood test requests across all locations in Wales to be linked.

CA-AKI was classified as patients with an e-alert generated in a non-inpatient setting. We further defined these groups as Primary Care acquired AKI (PC-AKI) and non-Primary Care acquired AKI (non-PC CA-AKI). Progression of AKI was defined as a peak AKI stage higher than that associated with incident e-alert or for stage 3 alerts an increase ≥50% from the SCr generating the alert. Hospitalization was defined as a measurement of renal function in a hospital setting within 7 days following the AKI e-alert.

Mortality data were collected from the Welsh Demographic Service.[24] Renal outcome analysis required patients to have 90 day follow up data available. Non-recovery was defined as achievement of a SCr value closest to and within 90 days still in keeping with the definition of AKI in comparisons to baseline SCr values. Pre-existing chronic kidney disease (PeCKD) was defined as an eGFR (calculated by CKDEpi eGFR formula) <60 ml/min/1.73m$^2$ derived from the baseline SCr. A worsening eGFR was calculated using the eGFR value closest to and within 90 days and was defined by a decline from baseline eGFR of >15% or >5 ml/min/1.73m$^2$.

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. P values less than 0.05 were considered statistically significant differences.

## Results

### Comparison of primary care and non-primary care community acquired AKI

There were 22 723 CA-AKI alerts in a total of 21 093 patients, of which 6 534 (28.8%) were generated by tests requested in Primary care (PC-AKI). Of the non-primary care community alerts (non-PC CA-AKI) 69% were generated at the hospital front door (Accident & Emergency and Acute assessment units) 19% in outpatient settings and the remainder in day case units. 37.6% of CA-AKI episodes included multiple alerts (Mean number of repeat alerts during episode = 2.1). For comparison over the same time period there were 19 314 incident episodes of HA-AKI.

There was a higher proportion of females and patients with pre-existing CKD for PC-AKI compared to non-PC CA-AKI. For both groups, the majority of alerts were AKI stage 1. There was however a greater proportion of PC-AKI of AKI stage 1 and less AKI 2/3 compared to non-PC CA-AKI. The proportion of those progressing to a worse stage of AKI following the alert was not significantly different between the two groups.

In PC-AKI, a higher proportion of alerts were based on rule 3 with a higher proportion of non-PC CA-AKI based on a baseline renal function derived from a more recent test results (rules 1 and 2). For PC-AKI and non-PC CA-AKI patients 4.6% and 7.7%

had a blood test result requested in primary care in the preceding 7 days.

Overall 90-day mortality for all CA-AKI was 24.0% and was lower for PC-AKI (15.4%) compared to non-PC CA-AKI (27.5%, $P < 0.001$) (Table 1). In contrast in the surviving group renal outcome was worse following PC-AKI with a higher proportion of 'non-recovery' and a greater proportion of those with pre-existing CKD with a significant decline in renal function at 90 days. For patients surviving to 90 days, the time to repeat renal function test after the incident alert (taken as a surrogate marker of action/recognition of the alert) was shorter for those who recovered renal function to baseline both for PC-AKI (12.9 ± 16.9 recovered vs. 16.8 ± 21.6 days, non-recovered, $P < 0.001$) and non-PC CA-AKI (6.8 ± 14.2 vs. 11.0 ± 14.8, $P < 0.001$) although for both outcome groups the time to repeat was significantly longer for PC-AKI compared to non-PC CA-AKI ($P < 0.001$ for all).

## Relationship between AKI alert and hospital admission in primary care

Of all patients with an AKI alert in primary care only 22.3% were admitted to hospital within 7 days of the alert. A comparison of patients with an alert in primary care who were admitted and those not admitted within 7 days of the alert is shown in Table 2. PC-AKI patients admitted were significantly older than those not admitted and there was a higher proportion of male patients and patients with pre-existing CKD.

Hospitalization was associated with a higher proportion AKI stage 2 and 3 and a higher proportion of patients progressing to a higher AKI stage than the stage associated with the alert (Table 2). Reflecting the greater disease severity hospitalization was associated with a higher mortality. Although non-admission was associated with lower mortality, in the surviving patients, non-admission was associated with worse renal outcomes (Table 2) compared to surviving patients admitted following an AKI alert (non-recovery 21.6% vs. 18.1%, $P = 0.01$, progression of pre-existing CKD 58.3% vs. 40.5%, $P < 0.001$).

## Responses to an AKI alert in primary care

For PC-AKI, 49.1% had a repeat test requested within 7 days (Table 3). 23.5% of repeat bloods were requested in primary care within 7 days of the incident alert, following which 10.8% were admitted within 7 days of the repeat (representing 8.6% of all PC-AKI leading to admission). 18.5% of results from tests repeated in primary care within 7 days demonstrated deterioration in renal function compared to the alerting result.

For PC-AKI, 25.6% had a repeat measurement of renal function within 7 days, but not in primary care (47.6% as hospital in-patients, 41.1% in A&E, and the remainder in a day case or hospital outpatient setting). These had a greater proportion of stage AKI stage 2 and 3 than the incident alert than the group repeated in primary care. In this group 43.2% demonstrated further deterioration and 83.0% were admitted within 7 days of repeat. This accounts for 71.9% of all PC-AKI admitted, and 89.3% of all PC-AKI admitted within 7 days of alerting.

A further 31.6% of PC-AKI had a repeat in primary care beyond 7 days of the alert. Mean time to repeat for this group was

**Table 1.** Characteristics of PC-AKI cohort vs. non-PC CA-AKI and HA-AKI cohorts

| | PC-AKI | Non-PC CA-AKI | P value |
|---|---|---|---|
| *n* (% of incident episodes) | 6534 (13.9) | 16189 (34.4) | |
| Mean age ± SD (yr) | 72.2 ± 23.9 | 70.3 ± 24.9 | |
| Male % (*n*) | 41.7 (2725) | 47.9 (7749) | P < 0.001 |
| Pre-existing CKD, % (*n*) | 43.2 (2816) | 34.6 (5588) | P < 0.001 |
| Mean baseline SCr ± SD (μmol/l) | 95.8 ± 51.4 | 92.1 ± 54.6 | |
| Mean alert SCr ± SD (μmol/l) | 182.2 ± 130.3 | 185.2 ± 142.2 | |
| Subsequent test in Primary Care, % (*n*) | 55.2 (3604) | 6.9 (1111) | P < 0.001 |
| % repeat measurement < 7 days | 49.1% | 78.0% | P < 0.001 |
| Hospitalization within 7 days of alert, % (*n*) | 22.3 (1459) | 66.2 (10713) | P < 0.001 |
| 90-day mortality, *n* (%) | 878 (15.4) | 3861 (27.5) | P < 0.001 |
| Non-recovery, *n* (%) | 1076 (20.9) | 1768 (15.2) | P < 0.001 |
| Worsening eGFR among patients with PeCKD, *n* (%) | 1220 (53.4) | 1567 (40.6) | P < 0.001 |
| AKI Severity, % (*n*) | | | |
| Stage 1 | 78.3 (5119) | 70.9 (11478) | P < 0.001 |
| Stage 2 | 12.5 (818) | 17.7 (2873) | |
| Stage 3 | 9.1 (597) | 11.4 (1838) | |
| Progression of AKI, % (*n*) | 17.8 (1161) | 19.0 (3082) | n/s |
| Mean peak SCr ±SD (μmol/l) | 209.0 ± 160.1 | 212.2 ± 167.1 | |
| Peak AKI Stage, % (*n*) | | | |
| Stage 1 | 63.9 (4177) | 55.8 (9034) | P < 0.001 |
| Stage 2 | 19.6 (1281) | 23.8 (3850) | |
| Stage 3 | 16.5 (1076) | 20.4 (3305) | |
| AKI rule, % (*n*) | | | |
| Rule 1 | 1.1 (69) | 4.8 (775) | P < 0.001 |
| Rule 2 | 3.8 (247) | 12.5 (2020) | |
| Rule 3 | 95.2 (6218) | 82.7 (13394) | |

Data on patient sex were missing for 4 episodes of the non-PC CA-AKI cohort and excluded from analysis of the sex variable. Baseline eGFR data were missing for 138 episodes (18, PC-AKI; 120, Non-PC CA-AKI) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 19 753 episodes (5709, PC-AKI; 14044, Non-PC CA-AKI). SCr follow up data was available for 16824 episodes (5161, PC-AKI; 11663, Non-PC CA-AKI) and included in analysis of the non-recovery variable. eGFR follow up data was available for 6148 episodes by patients with pre existing CKD (2285, PC-AKI; 3863, Non-PC CA-AKI) and included in analysis of the worsening eGFR variable. PC-AKI, Primary Care acquired AKI; Non-PC CA-AKI, Non-Primary Care Community acquired AKI; PeCKD, pre existing chronic kidney disease; SCr, Serum creatinine.

Table 2. Characteristics of Hospitalized PC-AKI cohort vs. non-hospitalized PC-AKI cohort

| | Hosp. PC-AKI | Non-hosp. PC-AKI | |
|---|---|---|---|
| *n* (% of AKI incident alerts) | 1459 (22.3) | 5075 (77.7) | |
| Mean age ± SD (yr) | 74.8 ± 13.5 | 71.5 ± 16.6 | |
| Male % (*n*) | 49.3 (719) | 39.5 (2006) | P < 0.001 |
| Pre-existing CKD, % (*n*) | 59.7 (869) | 38.5 (1947) | P < 0.001 |
| Mean baseline SCr ± SD (μmol/l) | 114.5 ± 57.9 | 90.4 ± 48.0 | |
| Mean baseline eGFR ± SD (ml/min/1.73m$^2$) | 56.8 ± 25.3 | 71.3 ± 29.2 | |
| Mean alert SCr ± SD (μmol/l) | 263.5 ± 181.8 | 158.9 ± 99.5 | |
| % repeat measurement < 7 days | 48.5% | 13.6% | P < 0.001 |
| 90-day mortality, *n* (%) | 391 (30.3) | 487 (11.0) | P < 0.001 |
| Non-recovery, n (%) | 192 (18.1) | 884 (21.6) | P = 0.01 |
| Worsening eGFR among patients with PeCKD, *n* (%) | 257 (40.5) | 963 (58.3) | P < 0.001 |
| AKI Severity, % (*n*) | | | |
| Stage 1 | 54.8 (800) | 85.1 (4319) | P < 0.001 |
| Stage 2 | 20.3 (296) | 10.3 (522) | |
| Stage 3 | 24.9 (363) | 4.6 (234) | |
| Progression of AKI, % (*n*) | 28.9 (422) | 14.6 (739) | P < 0.001 |
| Mean peak SCr ± SD (μmol/l) | 312.0 ± 207.6 | 179.5 ± 129.3 | |
| Peak AKI Stage, % (*n*) | | | |
| Stage 1 | 34.0 (497) | 72.5 (3680) | P < 0.001 |
| Stage 2 | 28.0 (408) | 17.2 (873) | |
| Stage 3 | 38.0 (554) | 10.3 (522) | |
| AKI rule, % (*n*) | | | |
| Rule 1 | 0.8 (12) | 1.1 (57) | n/s |
| Rule 2 | 4.1 (60) | 3.7 (187) | |
| Rule 3 | 95.1 (1387) | 95.2 (4831) | |

Baseline eGFR data were missing for 18 episodes (4, Hosp. PC-AKI; 14, Non-hosp. PC-AKI) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 5709 episodes (1292, Hosp. PC-AKI; 4417, Non-hosp. PC-AKI). SCr follow up data was available for 16824 episodes (1292, Hosp. PC-AKI; 4417, Non-hosp. PC-AKI) and included in analysis of the non-recovery variable. eGFR follow up data was available for 6148 episodes by patients with PeCKD (1292, Hosp. PC-AKI; 4417, Non-hosp. PC-AKI) and included in analysis of the worsening eGFR variable. Hosp. PC-AKI, Hospitalized Primary Care acquired AKI; Non-hosp. PC-AKI, non-hospitalized Primary Care acquired AKI; PeCKD, pre existing chronic kidney disease; SCr, Serum creatinine.

Table 3. Characteristics of PC-AKI subcategories by time and place of repeat measurement of renal function

| | PC < 7d | Non-PC <7d | PC ≥ 7d | Non-PC ≥7d | No repeat |
|---|---|---|---|---|---|
| *n* (% of PC-AKI incident episodes) | 1536 (23.5) | 1675 (25.6) | 2068 (31.7) | 707 (10.8) | 548 (8.4) |
| Mean age ± SD (yr) | 74.2 ± 14.3 | 74.4 ± 13.9 | 72.4 ± 15.5 | 70.2 ± 16.8 | 61.6 ± 22.2 |
| Male,% (*n*) | 40.4 (620) | 48.6 (814) | 39.7 (821) | 42.0 (297) | 31.6 (173) |
| Pre-existing CKD, % (*n*) | 51.1 (783) | 58.0 (968) | 35.7 (738) | 33.4 (235) | 16.9 (92) |
| AKI Severity, % (*n*) | | | | | |
| Stage 1 | 79.7 (1224) | 57.8 (968) | 89.4 (1849) | 84.9 (600) | 87.2 (478) |
| Stage 2 | 15.4 (237) | 18.7 (313) | 8.8 (182) | 6.8 (48) | 6.9 (38) |
| Stage 3 | 4.9 (75) | 23.5 (394) | 1.8 (37) | 8.3 (59) | 5.8 (32) |
| Mean time to repeat ± SD (days) | 3.9 ± 1.9 | 1.8 ± 1.7 | 21.9 ± 17.9 | 31.0 ± 22.2 | |
| Repeat SCr > than Alert SCr, % (*n*) | 18.5 (284) | 43.2 (724) | 17.4 (359) | 28.7 (203) | |
| Hospitalization within 7 days of repeat, % (*n*) | 10.8 (166) | 83.0 (1391) | 4.0 (83) | 41.7 (295) | |
| 90-day mortality, *n* (%) | 153 (11.3) | 441 (29.9) | 119 (6.6) | 97 (16.1) | 68 (13.9) |

Baseline eGFR data were missing for 18 episodes (3, PC<7d; 6, Non-PC<7d; 2, PC≥7d; 3, Non-PC≥7d; 4, No repeat) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 5709 episodes (1355, PC<7d; 1475, Non-PC<7d; 1790, PC≥7d; 601, Non-PC≥7d; 488, No repeat). PC <7d, Repeat measurement of renal function within 7 days in Primary Care; Non-PC <7d, Repeat measurement of renal function within 7 days not in Primary Care; PC≥7d, Repeat measurement of renal function within between 7 and 90 days in Primary Care; Non-PC≥7d, Repeat measurement of renal function within between 7 and 90 days not in Primary Care; No repeat, No repeat measurement of renal function during 90 day episode; PC-AKI, Primary Care acquired AKI; PeCKD, pre existing chronic kidney disease; SCr, Serum creatinine.

21.9 ± 17.9 days. Of these a further deterioration was reported in 17.4%, and admission within 7 days of this repeat occurred in only 4.0%. For 10.8% of PC-AKI a repeat was carried out beyond 7 days but not in primary care (34.8% in A&E, 28.9% as hospital outpatients, 19.5% as hospital in-patient, and the remainder in a day case setting). Of these 28.7% of the repeated demonstrated a further deterioration in renal function and admission (within 7 days) followed the repeated measurement in 41.7% of cases.

8.4% of PC-AKI had no recorded repeated measurement of renal function (within 90 days of alerting). 90-day mortality for this group was 13.9%.

In the surviving cohorts those with late repeated measurement of renal function (repeat >7 days) there was significantly

more non-recovery (24.0% vs. 17.9% $P < 0.001$) and more progression in those with pre-existing CKD at 90 days (63.3% vs. 47.0%, $P < 0.001$) than in patients who had an early repeat measurement of renal function.

## Discussion

Whilst AKI is recognized as being associated with increased healthcare utilization and poor health outcomes in the context of hospital settings, currently there is very little information focused on the detection and management of AKI in general practice. Although use of creatinine based definitions of AKI has limitations, the introduction of a national algorithm provides a means of alerting clinicians of significant changes in renal function indicative of AKI. Very little information is however available regarding the significance of AKI e-alerts in primary care, although implementation of automated primary care alerts has been demonstrated to be both technically feasible and influence primary care clinicians behaviour.[17]

The data demonstrate that roughly two thirds of all community acquired AKI alerting patients, present directly to the hospital front door. The role of primary care in the identification of acute illness and referral of these patients to the hospital is not apparent from our data, and they likely represent a mixture of self referrals and GP referrals to the hospital front door without a blood test. It is however of note that very few patients with non–PC CA-AKI have a blood test in primary care in the 7 days preceding the alert. 66% of CA-AKI patients were admitted directly to an in-patient setting which represents 88% of all CA-AKI admitted to hospital within 7 days. The remaining third of CA-AKI was generated following a blood test requested in primary care. Whilst these patients have lower 90-day mortality than the non-PC CA-AKI group, renal outcome in the surviving cohort was significantly worse.

For the alerting patients identified in primary care, within the hospitalized group there were a higher proportion of patients with AKI stage 2 and 3, and a higher proportion of patients with a serum creatinine which continued to rise following the incident alert. This suggests that that most severely ill are identified and admitted appropriately. For these patients there are two routes for admission related to an 'action' within 7 days, either an alert in primary care followed by attendance at A&E, or a second blood test in primary care within 7 days of an alert followed by hospital admission. Whilst the vast majority of PC-AKI related admissions occur following a repeat check of renal function at the hospital front door, this may represent an appropriate response with the alert triggering referral to the hospital front door.

Whilst those with the most severe illness seemingly are admitted to hospital, of concern is the significantly worse renal outcome in the PC-AKI group who survive the acute episode compared to non-PC CA-AKI cohort. In this study, we selected an arbitrary cut off of a repeat measurement of renal function within 7 days (in any setting) as an indication of early 'response' to AKI e-alerts transmitted in a General Practice setting. For all PC-AKI, a worse renal outcome was seen in those retested later than 7 days following the alert compared to those retested within 7 days. This is despite a higher admission rate in patients who have a repeated blood test within 7 days and a higher proportion of more severe AKI stage at presentation. For PC-AKI, renal outcome was worse for those not admitted to hospital, in which there were significantly fewer patients retested within 7 days of the alert (13.6% vs. 48.5%). Similarly, significantly fewer PC-AKI are retested within 7 days than non-PC CA-AKI, with a better renal outcome seen in the latter group (49.1% vs. 78.0%). Late response as measured by a delay beyond 7 days for a repeat measurement of renal function was therefore an indicator of worse renal outcome in patients surviving an episode of AKI highlighted by an e-alert.

Currently, there are no specific guidelines on the management of AKI patients in the community nor the appropriate response to an electronic AKI alert in this setting. For AKI, the National Institute for Health and Care Excellence (NICE) guidelines recommend that a repeat blood sample is taken within 2 weeks to exclude AKI with new fall in glomerular filtration rate is detected.[25] Our data would suggest that 7 days would be a more appropriate response time, with early 'response' (either a repeat measurement of renal function or referral for review within 7 days), being associated with improved renal outcome. A key consideration for primary care is the method of communication of the alert to the requesting clinician, as the introduction of e-alerts' in isolation are unlikely to improve outcomes[26] Recent research suggests that delivery of an AKI warning stage results results through interruptive methods is appropriate and acceptable to clinicians.[27] Our current practice is that all AKI's are telephoned to primary Care, unless passed 18.30 pm, when only stage 2 and 3 are phoned (as per request and agreement by Primary care colleagues). In this situation, AKI stage 1 will be phoned the next morning.

Agreed definitions define AKI based on changes in creatinine that are presumed to have occurred within the preceding 7 days.[9] Not all patients have had blood tests within the last week, which is a particular issue in the community and primary care. The national algorithm has adopted a pragmatic approach to generate e-alerts which utilizes look-back periods as long as 1 year. Our data highlight that in a community setting the vast majority of electronic alerts are based on a baseline derived from the median creatinine from the preceding 365 days (Rule 3). The data show significant adverse outcomes both in terms of patient mortality and renal outcome which suggest that his approach offers and acceptable trade–off between identifying all clinical relevant AKI patients and misclassifying patients to generate and alert which is useful and clinically relevant. It should be notted that any patient presenting with AKI but with no measurement of renal function in the previous 365 days will not be identified by our current alogithim. An alternative suggestion has been the use of population based estimated reference creatinine measures,[28] however currently in our clinical setting for these patients when a creatinine value is above the reference range, no AKI alert is issued but a message to highlight the rasied value accompanies the result report.

Although this study is the first to describe AKI highlighted by an automated electronic alert within primary care, it is important emphasize that our intention is not to characterize AKI but rather to delineate the significance of an electronic alert. The data lacks clinical context, race, the detail of the cause of AKI, and the cause of death. In addition, there is no linkage to primary care data sets and therefore the clinical response cannot be captured. Despite these limitations our study provides the first large scale description of the significance of AKI e-alerts in primary care.

The data demonstrate the clinical utility of AKI e-alerts in primary care and also identifies potential deficiencies in care. Although patients with the most severe degree of renal injury are admitted to hospital, patients in which AKI is highlighted by a test requested in primary care have worse renal outcomes. It is of note that less than half of patients highlighted by alerts in primary care are retested within 7 days of alerting.

Furthermore, delayed response to the alert is associated with a significantly worse renal outcome. In conclusion, we recommend that a clinical review, or referral together with a repeat measurement of renal function within 7 days should be considered an appropriate response to AKI e-alerts in primary care.

## Supplementary material

Supplementary material is available at *QJMED* online.

*Conflict of interest*: None declared.

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**Appendix 3.3:** Published work 3 related to this thesis:

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

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ABSTRACT

*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:* The study provides a nationwide characterisation of AKI in ICU highlighting the high incidence and its impact on patient outcome. The data also suggests that within the cohort of AKI patients treated in the ICU there are significant differences in the presentation and outcome between those patients that require transfer to the ICU after AKI is identified and those who develop AKI following ICU admission. Moreover, the study demonstrates that 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.



## 1. 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 an adaptation of the Kidney Disease: Improving Global Outcomes (KDIGO) change in creatinine diagnostic criteria has been agreed

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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 48 h. In order to understand the possible implication of an AKI e-alert in the context of the ICU, 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.

## 2. Methods

### 2.1. 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".

### 2.2. 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 Fig. 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 >26 μmol/l increase in SCr within the previous 48 h 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]. When an AKI e-alert is triggered, the Laboratory Information Management System automatically populates a separately named AKI e-alert database with the appropriate data.

### 2.3. Data collection

Data were collected for all cases of adult (≥ 18 yrs of age) AKI in Wales between November 2013 and April 2016. An incident episode was defined as 90 days, thus patients could have multiple episodes i.e. any AKI e-alert for the same patient within 90 days of the incident alert was not considered a new episode. As a result of this, it was possible for patients to have multiple episodes. 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, where ICU is defined as the patient type 'ITU & High Dependency' attached to a blood test request in the all Wales Laboratory Information Management System.

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-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. Nonrecovery was defined as achievement of an SCr value closest to and within 90 days, still consistent with the definition of AKI compared with baseline SCr values. Pre-existing chronic kidney disease (PeCKD) was defined as an eGFR (CKDEpi eGFR (15)) <60 ml/min/1.73 $m^2$ 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.

## 3. Results

We observed a total of 146,512 alerts, representing 47,090 incident AKI alerts. 10.0% (4746) of all episodes were associated with ICU admission and were generated by some 4690 individual patients. The majority of patients (98.9%) generated only one episode that required the services of ICU, 54 patients generated 2 episodes, and 1 patient generated 3 episodes. 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.

### 3.1. Comparison of AKI alerts generated in the community, in a hospital inpatient setting and on the ICU

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, 2318 (48.8%) alerted in ICU. 2428 (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 patients had a measurement of renal function as an inpatient in the preceding 9.8 ± 8.6 days, and 20.1% had a measurement of renal function in an A&E setting in the preceding 4.9 ± 6.9 days. This finding suggests the CA-AKI cohort contains a proportion of hospital re-attendance and re-admissions.

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 ($p < 0.001$).

**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/1.73 $m^2$) | 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.

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 ($p = 0.01$). Overall survival was also better for the cohort of patients whose AKI was identified on ICU compared to those patients transferred to ICU following identification of their AKI (Fig. 1A). For the whole cohort 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; $p < 0.001$). Whilst survival was associated with AKI stage for those patients whose AKI was identified in ICU, this association was not present in patients transferred to ICU following identification of their AKI (Fig. 1B&C). 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; $p < 0.001$).

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%).

### 3.2. 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 $p = 0.04$).

## 4. 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 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.

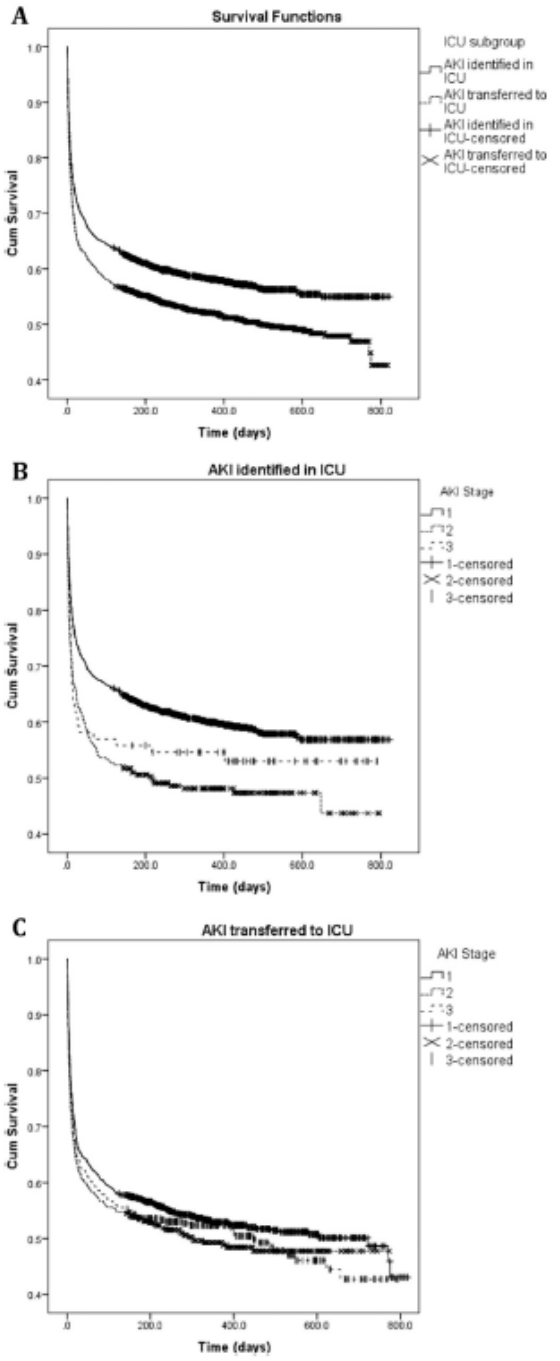


**Fig. 1.** Kaplan-Meier survival curves for AKI patients requiring ICU stratified by ICU subgroup. [A] AKI patients identified in ICU and AKI patients transferred to ICU. [B] AKI patients identified in ICU for AKI stages 1, 2 and 3. [C] AKI patients transferred to ICU for AKI stages 1, 2 and 3. ICU, Intensive Care Unit.

**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 |
| Stage 2 | 13.6 (315) | 18.0 (150)* | 21.7 (298) *# | #p < 0.001 vs. HA-AKI |
| 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<br>#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<br>†p = 0.009 vs. in-ICU<br>#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.

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, nonrecovery 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 short term patient survival but does not impact longer term renal outcome, which is in contrast to non-ICU populations [23]. We speculate that possible reasons for this might include more frequent monitoring

**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 |
| Stage 2 | | 19.5 (345)* | 21.6 (471)*# | #p < 0.001 vs. Rule 2 |
| 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<br>#p < 0.001 vs. Rule 1 |
| Recovery, % (n) | 89.5 (485) | 74.2 (1136)* | 86.1 (1184)#† | *p < 0.001 vs Rule1<br>#p = 0.04 vs. Rule 1<br>†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.

in ITU, and better immediate care in ITU compared to other healthcare settings.

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 HA-AKI and CA-AKI transferred to ICU following 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-h 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 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 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 comorbidity 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 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.

In summary, the study provides a nationwide characterisation of AKI in ICU, highlighting the high incidence and its impact on patient outcome. The data also suggests that within the cohort of AKI patients treated in the ICU there are significant differences in the presentation and outcome between those patients that require transfer to the ICU after AKI is identified and those who develop AKI following ICU admission. Moreover, 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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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.

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## Disclosures

There are no competing interests.

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**Appendix 3.4:** Published work 4 related to this thesis:

Gubb *et al*. (2020) 'Acute Kidney Injury in Children Based on Electronic Alerts', Journal of Pediatrics

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# Acute Kidney Injury in Children Based on Electronic Alerts

Samuel Gubb[1], Jennifer Holmes, MSc[2], Graham Smith, MD[3], John Geen, PhD[4], John Williams, MD[1], Kieron Donovan, MD[2], and Aled O. Phillips, MD[1]

**Objective** To define the incidence and outcome of acute kidney injury (AKI) in pediatrics using data collected from a national electronic alert system.

**Study design** A prospective national cohort study was undertaken to collect data on all cases of pediatric 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. Of the patients, 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. Thirty-day mortality was 1.7% but was significantly higher in hospital-acquired AKI (2.1%), compared with community-acquired AKI (0.8%, $P < .001$) 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 community-acquired AKI (69.7%) compared with hospital-acquired AKI (43.0%, $P < .001$), and higher in patients alerting with patients triggering with a creatinine within the reference range (48.4% vs 24.5%, $P < .001$). The majority of patients (84.7%) experienced only 1 AKI episode. Repeated episodes of AKI were associated with increased 30-mortaltiy (11.6% vs 4.6%, $P < .001$) and higher residual renal impairment (13.3% vs 5.4%, $P < .001$).

**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 (SCr), triggered by a SCr level that may be interpreted as being normal despite a significant increase from the baseline for the patient. *(J Pediatr 2020;220:14-20)*.

See editorial, p 9

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

## Methods

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

The Welsh electronic AKI reporting system[4] utilizes the all Wales Laboratory Information Management System (InterSystems TrakCare Laboratory, Windsor, UK) 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 Kidney Disease Improving Global Outcomes AKI staging criteria (**Figure 1**; available at www.jpeds.com). A summary of the definitions of AKI stages is shown in **Table I** (available at www.jpeds.com). Stage 1 AKI represents an increase of SCr levels by ≥26 μmol/L or an increase 1.5-1.9 times the reference creatinine value. Stage 2 represents an increase 2-2.9 fold the reference creatinine value and stage 3 AKI ≥3 times the reference creatinine value or a rise of ≥1.5 baseline to >354 mmol/L. AKI alerts are generated by applying 3 "rules" based on the time period from which the baseline creatinine level is obtained. The e-alert rule and the comment accompanying the e-alert is shown in **Table II**

| | |
|---|---|
| AKI | acute kidney injury |
| CA | Community-acquired |
| CKD | Chronic kidney disease |
| HA | Hospital-acquired |
| WIMD | Welsh Index of Multiple Deprivation |
| SCr | Serum creatinine |

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(available at www.jpeds.com). Rule 2 alerts represent a ≥50% increase in SCr value within 7 days, a rule 3 alert a ≥50% increase in SCr value from the median of results of the previous 8-365 days, and rule 1 alerts a >26 μmol/L increase in SCr value within the previous 48 hours but only if rule 2 and rule 3 are not satisfied. The e-alert code together with the comment that accompanies the e-alert is shown in **Table III** (available at www.jpeds.com). 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 SCr value 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, standardized using isotope dilution mass spectrometry (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 levels related to dialysis. Data were collected on age, sex, 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 noninpatient settings were classified as community-acquired (CA)-AKI, this includes, primary care, and all noninpatient settings of secondary care. Patients were labeled 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 SCr value within the normal reference range, the SCr reference ranges for age and sex currently in use in Wales were used[13] (**Table IV**; available at www.jpeds.com).

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 SCr value during the episode no longer in keeping with the definition of AKI when compared with the baseline SCr 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 baseline SCr value, which generated the incident alert.

Social deprivation was determined by the Welsh Index of Multiple Deprivation (WIMD), which ranks each of 1909 geographic areas in Wales based on income, employment, health, education, access to services, community safety, physical environment, and housing to generate a WIMD score.[15] Patients were categorized 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 Office for National Statistics (ONS) Population Estimates,[14] using the total pediatric population in each of the geographic areas of residence from which the WIMD score was generated.

Statistical analyses were carried out using SPSS software v 20 (SPSS, Inc, Chicago, Illinois). The student *t* test was used for analysis of normally distributed data. Categorical data were compared using a Pearson $\chi^2$ test. Data are expressed as mean ± SD; *P* values of <.05 were considered statistically significant.

## Results

There were 2472 alerts in a total of 1719 patients (**Table V**), 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 2**, A), with the highest incidence rates associated with the highest measures of social deprivation (r = −0.91, 95% CI −0.94 to −0.87; $P < .001$).

Thirty-day mortality was 1.7% (**Table V**) and overall mortality was 5.67%. Higher mortality was associated with stage 2 or 3 AKI compared with stage 1 (3.9% vs 1.3%, $P < .001$). 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%, $P < .001$). The likelihood of a repeat measure of creatinine, was higher for patients presenting with stage 2 or 3 AKI compared with stage 1 (72.3% vs 59.1%, $P < .001$), 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 HA-AKI and CA-AKI

Compared with 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, $P < .001$), and had a higher proportion of males (HA-AKI: 55.1% vs CA-AKI: 44.3%, $P < .001$). There was no difference in severity of AKI as assessed by AKI stage at presentation between HA and CA groups.

Compared with CA-AKI, 30-day mortality was significantly higher for patients following HA-AKI (HA-AKI: 2.1% vs CA-AKI: 0.8%; $P < .01$). Mortality censored at 4 years was also significantly greater in the HA-AKI (HA-AKI: 7.4% vs CA-AKI: 1.9%, $P < .001$; **Figure 2**, B). 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%, $P < .05$).

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%, $P < .001$). 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, $P < .01$).

Accident and emergency, outpatients, and general practice accounted for 86.1% of all CA-AKI alerts (**Table VI**; available at www.jpeds.com). Admission to the hospital following a CA-AKI alert was highest following an accident and emergency alert (40.5%). There was no difference in

**Table V. Characteristics of the pediatric cohort**

| Variables | Whole cohort | HA | CA | *P* value HA vs CA |
|---|---|---|---|---|
| Number of episodes, n (% of whole cohort) | 2472 (100) | 1719 (69.5) | 753 (30.5) | <.001 |
| Number of patients, n (%) | 1942 (100) | 1323 (68.1) | 619 (31.9) | <.001 |
| Mean (median) age ± SD (y) | 7.3 (5) ± 6.1 | 6.3 (5) ± 5.7 | 9.4 (10) ± 6.3 | <.001 |
| Male, n (%) | 1003 (51.6) | 729 (55.1) | 724 (44.3) | <.001 |
| Pre-existing CKD, n (%) | 74 (3.8) | 54 (4.1) | 20 (3.2) | n/s |
| AKI stage 1, n (%) | 1635 (84.2) | 1118 (84.5) | 517 (83.5) | n/s |
| AKI stage 2, n (%) | 238 (12.3) | 157 (11.9) | 81 (13.1) | n/s |
| AKI stage 3, n (%) | 69 (3.6) | 48 (3.6) | 21 (3.4) | n/s |
| Admitted to hospital, n (%) | | | 137 (22.1) | |
| Repeat test within 30 d, n (%) | 1188 (61.2) | 922 (69.7) | 266 (43.0) | <.001 |
| Mean time to repeat ± SD (d) | 2.9 ± 5.3 | 2.7 ± 5.0 | 3.4 ± 6.0 | <.01 |
| 30-d mortality, n (%) | 33 (1.7) | 28 (2.1) | 5 (0.8) | <.05 |
| 30-d recovery, n (%) | 1010 (94.0) | 795 (95.0) | 215 (90.7) | <.05 |
| Mean time to 30-d recovery ± SD (d) | 4.1 ± 6.4 | 4.0 ± 6.2 | 4.5 ± 7.0 | n/s |

1868 patients (1281, HA; 587, CA) were included in analysis of the 30-day mortality variable; 1074 patients (837, HA; 237, CA) were included in analysis of the 30-day recovery variable. The index episode was used for patients with multiple episodes of AKI.

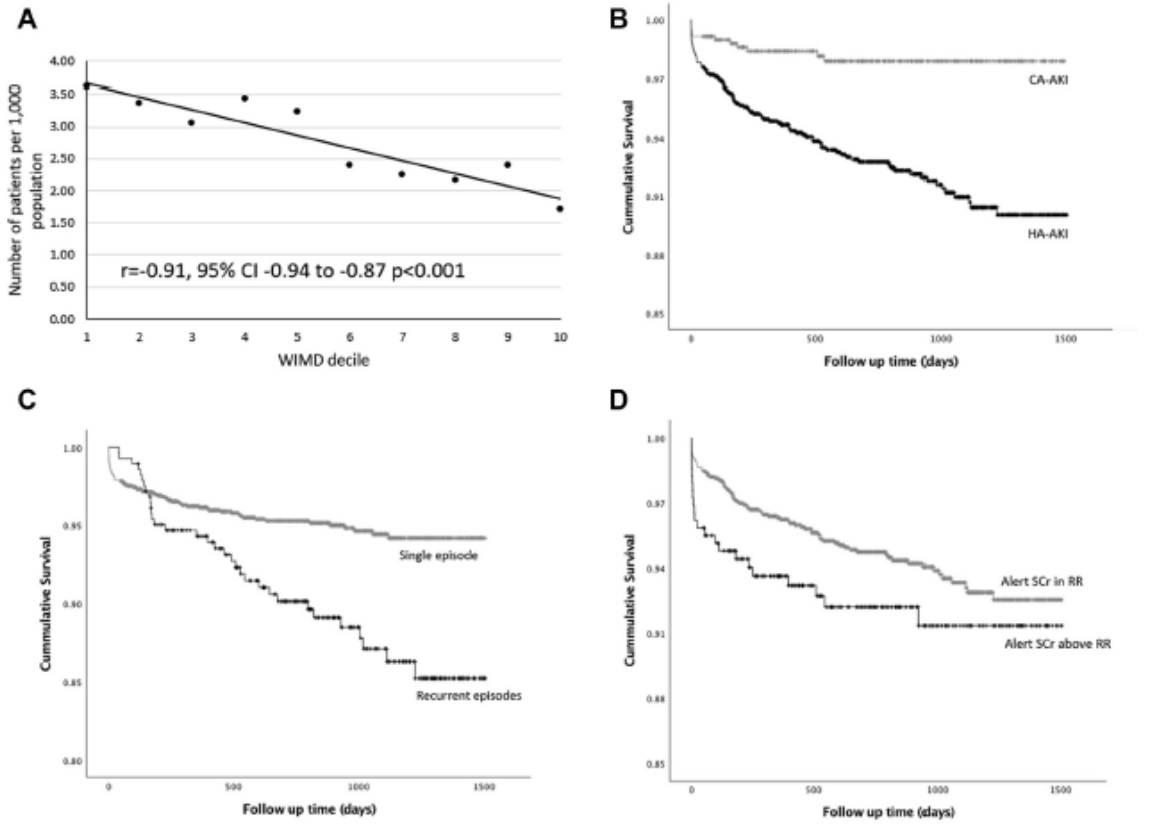


**Figure 2.** **A,** Negative association between the incidence of AKI and the index of social deprivation. In total, 175 patients with missing postcode data were excluded from analysis. WIMD where decile 1 is the most deprived and decile 10 is the least deprived. **B,** Kaplan Meier survival curves for HA-AKI vs 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. *WIMD*, Welsh Index of Multiple Deprivation; *RR*, reference range. The index episode was used for patients with multiple episodes of AKI.

**Table VII. Characteristics of patients who had a single episode of AKI vs patients who had recurrent episodes of AKI**

| Variables | One episode | Recurrent episodes | *P* value |
|---|---|---|---|
| Number of patients, n (% of whole cohort) | 1645 (84.7) | 297 (15.3) | |
| Mean (median) age ± SD (y) | 7.4 (6) ± 6.1 | 6.7 (5) ± 5.1 | n/s |
| AKI stage 1, n (%) | 1391 (84.1) | 244 (82.2) | n/s |
| AKI stage 2/3, n (%) | 254 (15.4) | 53 (17.9) | n/s |
| Hospital acquired, n (%) | 1104 (67.1) | 219 (73.7) | <.05* |
| Community acquired, n (%) | 541 (32.9) | 78 (26.3) | <.05* |
| Overall mortality, n (%) | 73 (4.6) | 33 (11.6) | <.001 |
| Overall recovery, n (%) | 807 (94.5) | 183 (86.7) | <.001 |
| Mean time to overall recovery ± SD (d) | 3.8 ± 5.9 | 5.4 ± 8.0 | <.001 |
| Repeat test within 30 d, n (%) | 950 (57.8) | 238 (80.1) | <.001 |
| Mean time to repeat ± SD (d) | 2.6 ± 4.8 | 3.9 ± 6.8 | <.001 |
| Mean number of episodes ± SD (range) | | 2.8 ± 1.4 (2-11) | |

1868 patients (1583, 1 episode; 285, recurrent episodes) were included in analysis of the overall mortality variable; 1065 patients (854, 1 episode; 211, recurrent episodes) were included in analysis of the overall recovery variable.
*P value is for comparison of HA vs CA for the "recurrent episodes" group. The index episode was used for patients with multiple episodes of AKI.

admission rates following outpatients or general practice alerts (14.0% vs 7.1%, $P > .05$). It is of note that all 9 patients admitted following a general practice alert presented with a stage 1 AKI alert, whereas 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 SCr 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 inpatient (36.2%, n = 55), following review at accident and emergency (19.7%, n = 30), or in outpatients (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 1 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 regard to multiple or singular episodes (Table VII). For surviving patients, nonrecovery 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%, $P = .16$). Multiple AKI episodes were more likely following an incident HA-AKI episode (73.7% vs 67.1%, $P < .05$).

Thirty-day mortality was higher in patients experiencing more than 1 AKI episode (11.6% vs 4.6%, $P < .001$). Similarly, mortality censored at 4 years, was significantly higher in the cohort with 2 or more AKI episodes (Figure 2, C). Repeated episodes of AKI were also associated with a lower rate of recovery of renal function (86.7% vs 94.5%, $P < .001$).

**Table VIII. 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**

| Variables | Alert SCr in RR | Alert SCr above RR | *P* value |
|---|---|---|---|
| Number of episodes, n (% of whole cohort) | 1441 (58.3) | 1031 (41.7) | <.001 |
| Number of patients, n (% of whole cohort) | 1164 (59.9) | 778 (40.1) | <.001 |
| Mean (median) age ± SD (y) | 6.6 (5) ± 6.1 | 8.3 (7) ± 6.0 | <.001 |
| AKI stage 1, n (%) | 1072 (92.1) | 563 (72.4) | <.001 |
| AKI stage 2/3, n (%) | 92 (7.9) | 215 (27.6) | <.001 |
| Hospital acquired, n (%) | 824 (70.8) | 499 (64.1) | <.01* |
| Community acquired, n (%) | 340 (29.2) | 279 (35.9) | <.01* |
| 30-d mortality, n (%) | 10 (0.9) | 23 (3.1) | <.001 |
| 30-d recovery, n (%) | 532 (96.7) | 478 (91.2) | <.001 |
| Mean time to 30-d recovery ± SD (d) | 4.2 ± 6.3 | 4.0 ± 6.5 | <.01 |
| Repeat test within 30 d, n (%) | 601 (51.6) | 587 (75.5) | <.001 |
| Mean time to repeat ± SD (d) | 3.4 ± 5.7 | 2.3 ± 4.8 | <.001 |

1868 patients (1128, Alert SCr in reference range; 740, Alert SCr above reference range) were included in analysis of the 30-day mortality variable; 1074 patients (550, Alert SCr in reference range; 524, Alert SCr above reference range) were included in analysis of the 30-day recovery variable.
*P value is for comparison of HA vs CA for both groups. The index episode was used for patients with multiple episodes of AKI.

### Significance of an AKI Alert Based on a SCr Value within the Reference Range

Using upper and lower SCr reference range values for age and sex, 58% of AKI alerts in this pediatric population occurs with a creatinine value within the reference range. There was no difference in age between the 2 groups (Table VIII), 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 value (27.6% vs 7.9%, $P < .001$). Ninety-two patients experienced AKI stage 2/3 with an alerting SCr value within the estimated reference range. An alert with a creatinine value above the estimated reference range was more common in HA-AKI compared with CA-AKI (64.1% vs 35.9%, $P < .01$). In the CA-AKI patients, those alerting with a creatinine value above the reference range were more likely to be admitted to hospital than those alerting within the estimated normal creatinine value range (34.1% vs 12.4%, $P < .001$).

Thirty-day mortality was higher in the abnormal creatinine value alert cohort (3.1% vs 0.9%, $P < .001$), similarly mortality censored at 4 years (Figure 2, D) was also higher in the abnormal creatinine value group ($P < .05$). Recovery (in the surviving group) was also lower in patients with an alerting SCr value above the reference range (91.2% vs 96.7%, $P < .001$).

For those with follow-up data, time to recovery was shorter in those alerting with a creatinine value above the reference range (4.0 ± 6.5 vs 4.2 ± 6.3 days, $P < .01$). 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%, $P < .001$), although it is of note that even in this cohort a significant proportion (24.5%) had no follow-up measurement.

## Discussion

AKI in children is associated with prolonged hospital stay,[1] higher inpatient mortality,[2] and a higher incidence of chronic renal dysfunction.[3] Although the epidemiology of adult AKI is well described, there are few reports describing pediatric AKI. Publications characterizing AKI predominantly rely on hospital coding or a retrospective review of hospital records to identify AKI cases,[16-19] resulting in underestimation of the true incidence of AKI. The reported incidence of AKI also varies depending on its definition. The centralized laboratory-based identification and alerting of AKI in Wales has allowed us to generate a national data set to provide characterization of the epidemiology of AKI in adults.[4-11]

Our reported incidence of AKI is significantly higher than previously reported in children.[2,20,21] This likely reflects the methodological differences with a reliance on coding and a focus on hospitalized cases. As expected for the whole cohort, the outcomes following AKI, both mortality and nonrecovery 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 with adults. Less than 20% of inpatients have repeated blood tests and measurement of SCr during an inpatient admission.[21] It is also likely that a lack of repeat measure of creatinine reflects a failure to recognize 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 comorbidities. In contrast for pediatric populations, previous studies in nonrenal illnesses suggest that social inequality likely reflects environmental and behavioral influences, such as housing conditions and overcrowding,[22,23] air-pollution,[24,25] poor diet, and sedentary behavior.[26-28] The majority of AKI cases do not represent intrinsic kidney disease but are the 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 socioeconomic 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 that 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. Although children with HA-AKI tended to be younger and male, 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 recognize the importance of the alert. This is supported by the lower numbers of patients 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 one-third of patients with CA-AKI have had a measure of renal function within a hospital setting in the 4 weeks prior to presentation with CA-AKI.[6] In this pediatric cohort, the data again demonstrate that a significant proportion of AKI labeled 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 labeled 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 outcomes[29] and increased risk of progressive chronic kidney disease (CKD).[30] In an adult population, roughly one-third of patients experience at least 1 AKI recurrence.[31] In this study, approximately 15% of children, experienced more than 1 AKI episode. This is significantly less than we have previously reported in an adult cohort and likely reflects the smaller burden of comorbidity in this younger patient group. In an adult population, we have used the presence of pre-existing CKD as a marker of comorbidity. Over 40% of adult AKI episodes represent AKI with pre-existing CKD.[4] In contrast, less than 5% of the pediatric population have pre-existing CKD. Although 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 one-half of the AKI alerts were generated with a trigger SCr value within the reference range. As expected, clinical outcomes were worse for those patients with an alerting creatinine value above the reference range. It is of note that cases of stage 2 and 3 AKI were identified with a creatinine value within the reference range. AKI episodes in this group, although having a better outcome, carry significant mortality and nonrecovery of renal function. Almost two-thirds of CA-AKI were related to an alerting creatinine value within the reference range. A repeat measure of creatinine was less likely if the triggering SCr value was within the reference range, with almost one-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 value in the reference range. Previous published data have demonstrated that even small increments of SCr values adversely impact clinical outcomes in adults[32-34] and children.[35] Our data, however, suggest that the significance of increases in SCr values 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.

Our findings should be qualified by limitations. As the e-alert system is information technology driven and is based on biochemical measures only, there is no clinical detail. As a result

we are unable to report on the cause of the AKI episodes or determine the level of patient comorbidity and associated primary diagnoses. In addition, we lack data on the need for renal replacement therapy 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 presenting with a raised creatinine level will not be included. Given that most children never have a SCr checked during their childhood, the pediatric population who has had a SCr 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 noted that SCr 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) and may have a substantially lower SCr value than normal. Although this is likely to represent a small number of children, it may also result in an underestimation of AKI rates in our study. Furthermore, children with such abnormalities are more likely to be in the population who can earn the AKI label in the reporting system because they are more likely than a general population of healthy children to have a SCr test in the preceding year. ■

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**Appendix 3.5:** Published work 5 related to this thesis:

Jones *et al*. (2020) 'Using electronic AKI alerts to define the epidemiology of acute kidney injury in renal transplants', Journal of Nephrology

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ORIGINAL ARTICLE

# Using electronic AKI alerts to define the epidemiology of acute kidney injury in renal transplants

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## Abstract

**Background** Little is known regarding the impact of acute kidney injury (AKI) on renal transplant outcome. Our aim was to define the incidence and outcome of AKI in renal transplant patients using data collected from a national AKI electronic alert system

**Methods** The study represents a prospective national cohort study collecting data on 1224 renal transplants recipients with a functioning renal transplant, between April 2015 and March 2019.

**Results** Four hundred forty patients experienced at least one episode of AKI giving an incidence rate of 35.4%. Sixty-four point seven% of episodes were AKI stage 1, 7.3% AKI stage 2 and 28% AKI stage 3. Only 6.2% of episodes occurred in the context of rejection. Forty-three point five% of AKI episodes were associated with sepsis. AKI was associated with pre-existing renal dysfunction, and a primary renal diagnosis of diabetic nephropathy. AKI was more prevalent in recipients from a donor after cardiac death (26.4% vs. 21.4%, $p<0.05$) compared to the non-AKI cohort. Following AKI, 30-day mortality was 19.8% and overall mortality was 34.8%, compared to 8.4% in the non AKI cohort (RR 4.06, 95% CI 3.1–5.3, $p<0.001$). Graft survival (GS), and death censored graft survival (DCGS) censored at 4 years, in the AKI cohort were significantly lower than in the non AKI group ($p<0.0001$ for GS and DCGS).

**Conclusion** The study provides a detailed characterisation of AKI in renal transplant recipients highlighting its significant negative impact on patient and graft survival.

**Keywords** Renal transplant · Acute kidney injury · Outcome · Graft survival

## Introduction

Acute Kidney Injury (AKI), is associated with increased patient morbidity and mortality [1, 2]. The majority of publications characterizing AKI are dependent on making and recording the diagnosis of AKI through either hospital coding or a retrospective review of hospital records [3–6]. An automated real time electronic (e)-alert system for AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) change in creatinine diagnostic criteria has been implemented across all areas of the National Health Service in England and Wales, with the aim of facilitating early identification and intervention, and the presumption that this will influence clinical outcomes. To generate the alert the all Wales Laboratory Information Management System (LIMS) (Intersystems TrakCare Lab) automatically compares measured serum creatinine (SCr) values on an individual patient against previous results on the system database. We developed a centralized data collection system based on these alerts, and previously published a comprehensive characterization of the incidence of AKI identified by an electronic alert, and its outcome in the general population of Wales [7–9].

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Data related to the incidence and outcome of AKI in the context of renal transplantation are scarce, and in the main rely on making and recording an accurate diagnosis of AKI through hospital coding or retrospective review of hospital records [10–12], and relate to relatively short follow up of patients following transplantation and relatively small patient numbers [13–15]. The most recent data however, using hospital discharge coding data, suggest that the incidence of hospitalisations for AKI among kidney transplant recipients is rising [10]. We have previously demonstrated that in the general population a focus on hospitalised patients with a diagnosis based on retrospective coding data leads to significant under-reporting of AKI compared to electronic AKI alerts [7, 8, 16].

The current study uses a national population-based data set to describe the incidence and outcome of AKI in renal transplant recipients with AKI identified by an automated biochemistry-based electronic AKI alert.

## Methods

Data from all Health boards in the National Health Service in Wales, representing a population of 3.06 million people, was collected from the LIMS on all patients aged 18 yrs or over between 1st April, 2015 and 31st March, 2019 that generated an AKI e-alert. The NHS Number, a unique reference number allocated to patients registered with the NHS in England, Wales and the Isle of Man, was used as the patient identifier to cross reference with the Welsh National Renal database, to identify prevalent transplant patients with and without AKI over the study period. This included any patient with a functioning kidney graft at any time during the study period. Only renal transplant recipients aged 18 years or older with a time since transplantation greater than 90 days were included. The study was approved under the terms of Service Evaluation Project Registration.

The AKI alert is generated by comparing in real time a current SCr value with historic SCr measurements for the same patient. It defines AKI according to KDIGO increase in creatinine parameters [7]. Patients were only included in the study if the AKI alert was generated from a baseline creatinine related to a functioning transplant, i.e. no patients had baseline generated from a creatinine related to a period on dialysis. We have previously demonstrated that this approach ensures collection of all AKI episodes highlighted by an electronic alert across the country, regardless of the clinical location, and excludes patients with end stage renal failure (ESRF), receiving renal replacement therapy (RRT). The AKI Alerts are displayed alongside the biochemical results on the pathology reporting system and consist of one of the following text statements which provide context to the change in creatinine for the receiver:

(a) Trigger ≥ 26 µmol/l increase in creatinine within 48 h, Associated alert; Acute Kidney Injury alert: rising creatinine within last 48 h.
(b) Trigger ≥ 50% increase in creatinine within 7 days; Associated alert; Acute Kidney Injury alert: rising creatinine within last 7 day.
(c) Trigger = 50% increase in serum creatinine against median result for 8–365 days, Associated alert; Acute Kidney Injury alert—creatinine increase over baseline value.

An AKI episode was defined as 30 days, with the first AKI alert defined as the incident alert. Any alert for the same patient within 30 days of the incident alert was not considered a new episode. For patients with multiple episodes, their first episode was defined as their index episode.

Data on patient mortality was collected from the Welsh Demographic Service [17]. Recovery of renal function was defined as a SCr value during the episode no longer in keeping with the definition of AKI when compared to the baseline SCr value associated with the same episode. Only surviving patients who had at least one SCr test during the episode were included in the recovery analysis. Pre-study baseline renal function for those transplant recipients with a transplant date of more than 90 days before the study start date of 1st April, 2015 was defined using the last SCr value recorded before the study start date. For all other transplant recipients, the last SCr value recorded before date of transplant + 90 days was used. Post-study renal function was defined as the latest SCr value recorded after the end of the study period. Estimated glomerular filtration rate (eGFR) was calculated using the CKDEpi eGFR formula. A greater than 15% deterioration in the eGFR or a deterioration in eGFR greater than 5 ml/min from the baseline renal function of the patient at the date of entry into the study was used to indicate a significant deterioration in renal function over the course of the study. Only those patients still living with a functioning graft at the end of the study period were included in the analysis of this variable.

Statistical analysis was carried out using SPSS software, version 25 (IBM SPSS, Chicago, IL). Student's *t* test was used for analysis of normally distributed data. Categorical data were compared using a Pearson Chi-squared test. Kaplan Meier analysis was used to estimate and compare survival of patient groups. Multivariate Binary Logistic Regression was used to assess the association of baseline SCr, AKI stage, Age at AKI, Age at transplant, Recurrent AKI, and Donor type with overall patient survival, overall patient and graft survival, and overall renal recovery from AKI.

## Results

In a total of 1224 renal transplants, 440 patients experienced at least one episode of AKI giving an incidence of AKI of 35.4% over the study period (Table 1). In total there were 937 episodes of AKI with roughly half (224) of the patients who experienced an AKI episode experiencing more than one AKI episode. For patients with multiple episodes, mean number of episodes was 3.2 ± 2.1. The majority (64.7%) of episodes were classified as AKI stage 1 at presentation, with 7.3% AKI stage 2 and 28% AKI stage 3.

The mean age of the AKI cohort of transplant recipients was no different to those with no AKI (47.2 ± 15.4 vs. 46.2 ± 14.7 yrs). There was no difference in gender distribution between the AKI and non-AKI patients (38.2% were female in the AKI vs. 35.3% in the non-AKI group, p = 0.3). Similarly, the average time since transplant to inclusion in the study was also no different between the AKI and non-AKI cohort (1942 ± 2350 vs. 1998 ± 2380 days). In contrast, the mean baseline serum creatinine was significantly higher in the AKI cohort compared to the non-AKI cohort (173.0 ± 127.2 vs. 128.1 ± 51.2 µmol/l). The aetiologies of underlying end-stage renal disease of transplant patients are shown in Table 1. Diabetic nephropathy as a primary renal diagnosis was more common in the AKI cohort. There were no differences in the distribution of all other primary diagnoses.

Within the AKI cohort there were significantly more patients receiving a transplant from a donor after cardiac death (26.4% vs. 21.4%, p < 0.05) and less from live related donation (23.6% vs. 33.7%, p < 0.001) compared to the non-AKI cohort.

The clinical locations of the blood test resulting in the incident AKI alert are shown in Fig. 1. Roughly half of the AKI episodes were associated with an alert related to a

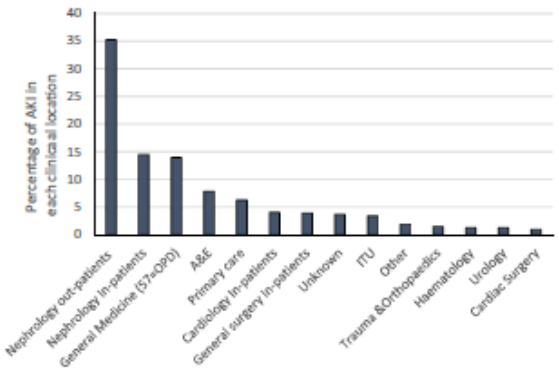


**Fig. 1** Clinical locations at which the blood test resulting in the AKI alert was generated

**Table 1** Characteristics of transplant patients who had AKI vs. patients who had no AKI

| | AKI | No AKI | p value |
|---|---|---|---|
| Number of patients, n (number of transplants) | 440 (440) | 771 (784) | |
| Number of AKI episodes | 937 | – | |
| Mean age at time of transplant ± SD (years) | 47.2 ± 15.5 | 46.2 ± 14.7 | p = NS |
| % Female | 38.2 | 35.3 | p = NS |
| Primary renal diagnosis % (n) | | | |
| Polycystic kidney disease | 12.5 (55) | 14.5 (112) | p = NS |
| IgA nephropathy | 11.8 (52) | 13.5 (104) | p = NS |
| Diabetic nephropathy | 14.1 (62) | 9.6 (76) | p = 0.026 |
| Reflux nephropathy | 6.1 (27) | 7.1 (55) | p = NS |
| Glomerulonephritis | 10.2 (45) | 11.4 (88) | p = NS |
| Primary FSGS | 3.2 (14) | 3.4 (26) | p = NS |
| Hypertensive nephrosclerosis | 2.5 (11) | 2.7 (21) | p = NS |
| Idiopathic membranous glomerulonephritis | 1.6 (7) | 1.4 (11) | p = NS |
| Other | 11.8 (52) | 14.1 (109) | |
| Unknown | 9.6 (42) | 7.4 (57) | |
| Diagnosis not recorded | 16.6 (73) | 14.5 (112) | |
| Time from transplant to start of study ± SD (days) | 1942 ± 2350 | 1998 ± 2380 | p = NS |
| Mean baseline Creatinine ± SD (mmol/l) | 173.0 ± 127.2 | 128.1 ± 51.2 | p < 0.001 |
| Donor type % (n=) | | | |
| Donor after brain death | 49.5 (218) | 44.9 (352) | p = NS |
| Donor after cardiac death | 26.4 (116) | 21.4 (168) | p < 0.05 |
| Live related donor | 23.6 (104) | 33.7 (264) | p < 0.001 |

nephrology request, the majority of which were a result of a blood test requested in a transplant out-patient setting. Of the remaining AKI episodes, the majority of alerts were reported following requests from general medical in-patients (7.9%), Accident and Emergency (7.9%), primary care (6.3%) and general medical out patients (6.1%).

## Natural history of AKI in renal transplant recipients (Table 2)

Following an AKI episode, 30-day mortality was 19.8% and overall mortality over the study period was 34.8%. Baseline serum creatinine was significantly higher in the cohort of AKI patients who died compared to the surviving patients (210.29 ± 173.1 vs. 153.5 ± 89.2 µmol/l, p = 0.0002). More than one episode of AKI was associated with higher overall patient mortality compared with patients with only one episode (41.1% vs. 28.2%, RR 1.5, 95% CI 1.1–1.9, p = 0.005). In those patients who survived an episode of AKI and had follow-up biochemistry data available, recovery of renal function occurred in 75% of episodes. In the surviving group severity of AKI was a determinant of recovery of renal function, which was lower in patients with incident stage 2 or 3 AKI alerts compared with stage 1 (56.8% vs. 70.5%, P < 0.001). There was no association between non-recovery of renal function and overall patient mortality, with a 29% mortality rate for those that recovered compared to 31.6% for those that did not. There was also no association between non-recovery and repeated AKI episodes, with 52.3% of patients that recovered their index episode experiencing at least one further episode, compared to 60.7% of those that did not recover their renal function in their index episode.

Multivariate Binary Logistic Regression showed that a lower baseline SCr (B = − 0.01, p < 0.001) and age at AKI (B = − 0.07, p < 0.001) were associated with an increased likelihood of overall patient survival, and patients with multiple AKI episodes were less likely to survive compared to those who had a single episode (OR = 0.47, 95% CI 0.30–0.75, p < 0.001). Similarly, a lower baseline SCr (B = − 0.01, p < 0.001) and age at AKI (B = − 0.07, p < 0.015) were also associated with an increased likelihood of overall patient and graft survival. Patients with AKI stage 3 were less likely to survive with a functioning graft compared to those with AKI stage 1 (OR = 0.46, 95% CI 0.25–0.86, p = 0.014), as was the case with patients with multiple AKI episodes compared to patients with a single episode (OR = 0.39, 95% CI 0.25–0.61, p < 0.001). Furthermore, a lower baseline SCr (B = − 0.01, p = 0.048) lower age at AKI (B = − 0.05, p = 0.011), and higher age at transplant (B = 0.05, p = 0.011) were associated with an increased likelihood of overall renal recovery from AKI, and patients with multiple AKI episodes were far less likely to recover compared to those who had a single episode (OR = 0.28, 95% CI 0.17–0.47, p < 0.001).

Our previous work in non-transplant associated AKI has demonstrated that a significant proportion of patients highlighted with an AKI alert do not have further monitoring of renal function. In this transplant recipient cohort 96.1% of the AKI episodes were associated with a repeat measure of renal function within 7 days of the alert, with a mean time to repeat of 3.8 ± 5.9 days. It should be noted however that in 37 episodes no repeat measure of renal function was requested within 7 days of the incident alert.

The clinical diagnosis associated with each AKI episode is shown in Table 3. Rejection was associated with only

**Table 2** Natural history of AKI in Renal Transplantation

| | Whole AKI cohort | CA-AKI | HA-AKI | p value CA vs. HA-AKI |
|---|---|---|---|---|
| Number of AKI episodes, n (% of whole cohort) | 937 | 538 (57.4) | 273 (29.1) | |
| Mean age at time of AKI ± SD (years) | 55.2 ± 14.7 | 53.2 ± 14.6 | 59.6 ± 13.2 | p < 0.001 |
| AKI stage 1, % (n) | 64.7 (606) | 64.5 (312) | 78.4 (214) | p < 0.001 |
| AKI stage 2, % (n) | 7.3 (68) | 7.8 (42) | 6.6 (18) | p = n/s |
| AKI stage 3, % (n) | 28.0 (263) | 34.2 (184) | 18.4 (41) | p < 0.001 |
| Outcome measures | | | | |
| 30-day mortality, % (n) | 19.8 (87) | 4.8 (26) | 16.8 (46) | p < 0.001 |
| Overall mortality, % (n) | 34.8 (153) | | | |
| 30-day recovery of renal function, % (n) | 75 (615) | 70.2 (340)ƒ | 81.8 (185) | p < 0.001 |
| Process measures | | | | |
| Repeat test within 30 days, % (n) | 96.1 (900) | 93.9 (505) | 98.8 (270) | p = 0.001 |
| Mean time to repeat ± SD (days) | 3.8 ± 5.9 | 5.5 ± 7.13 | 1.43 ± 1.87 | p < 0.001 |

Recovery of renal function included only surviving patients with available tests of follow-up renal function: 710 episodes were included in the 30-day recovery of renal function analysis (484 episodes, CA; 226 episodes, HA-AKI)

**Table 3** Clinical course by clinical diagnosis associated with AKI episode

| | Number of episodes (%) | Mean age ± SD (years) | AKI stage (% of episodes) | 30-day mortality, % (n) | 30-day recovery of renal function, % (n) |
|---|---|---|---|---|---|
| Non-rejection, n (%) | 692 (73.9) | 56.11 ± 14.5 | 1: 67.5<br>2: 9.1<br>3: 23.4 | 9.39 (65) | 79.7 (486) |
| Sepsis, n (%)<br>(Urinary)<br>(Respiratory) | 408 (43.5)<br>(171)<br>(11) | 56.38 ± 14.63 | 1: 67.9<br>2: 10.3<br>3: 21.8 | 8.3 (34) | 89.2 (364) |
| Dehydration | 142 | | | | |
| Cardiac | 27 | | | | |
| Obstruction | 16 | | | | |
| Recurrent disease | 14 | | | | |
| Contrast | 7 | | | | |
| Other | 65 | | | | |
| Rejection, n (%) | 58 (6.2) | 44.91 ± 16.3* | 1: 53.4*<br>2: 3.4<br>3: 43.1* | 5.17 (3) | 49.06 (26) |

Details of clinical diagnosis associated with AKI were not available for 187 episodes. Mortality data were available for 692 non-rejection episodes and 58 rejection episodes. Recovery of renal function included only surviving patients with available tests of follow-up renal function: for non-rejection AKI recovery included 608 episodes and for rejection 53 episodes. For the sepsis-associated AKI group mortality data were available for all 408 episodes, recovery of renal function included 364 episodes

*$p < 0.001$ compared to Non rejection AKI

6.2% of all episodes. This cohort was significantly younger than the non-rejection group, and had a higher proportion of AKI stage 3 at presentation. In the non-rejection cohort, the predominantly associated clinical diagnosis was sepsis, with urinary tract and respiratory infection accounting for the majority of cases. There were no differences in mortality between the rejection- and non-rejection-associated AKI episodes. Recovery of renal function was however significantly worse following rejection-associated AKI, reflecting the higher proportion of stage 3 AKI at presentation.

## Comparison of hospital- and community-acquired (HA)/(CA) transplant-associated AKI

CA-AKI accounted for 57.4% of all episodes (n = 538), of which hospitalisation following the alert occurred in only 37 episodes. Transplant out-patients' requests accounted for 61.3% of CA-AKI. The other major sources of CA-AKI alerts were Accident and Emergency (13.9%), Primary care (11.0%) and medical out-patients (10.6%).

HA-AKI accounted for 29.1% (273) of all transplant-associated AKI. For hospital-acquired AKI, the largest single cohort was reported following a blood test requested from the renal transplant in-patient ward (49.8%), followed by general medical in-patients (27.1%), cardiology in-patients (13.9%), general surgery in-patients (13.5%), and intensive treatment unit (ITU) (11.7%). The remaining 13.4% (126) of alerts were generated in an in-patient setting, but as no results were available for the previous 7 days it was not possible to confidently classify these as either CA- or HA-AKI.

The proportion of incident AKI alerts reported as AKI stage 3 was significantly higher in CA-AKI compared to HA-AKI (Table 2). Conversely the proportion of AKI stage 1 was lower in the CA-AKI group compared to HA-AKI. Compared to CA-AKI, 30-day mortality was significantly higher for patients following HA-AKI (HA-AKI: 16.8% vs. CA-AKI: 4.8%, $p = 0.001$). In contrast to mortality outcomes, for the surviving patients recovery of renal function at 30-days was significantly better following HA-AKI (HA-AKI; 81.8% vs. CA-AKI: 70.2%, $p < 0.001$). Within the CA-AKI cohort the mean time to repeat measurement was 5.5 ± 7.1 days; following 33 AKI episodes there were no repeat measures of renal function within 7 days of the alert. In contrast, in the HA AKI cohort, there were no repeat measures of renal function within 7 days following only 3 AKI episodes, and the average time to repeat was significantly shorter than in CA-AKI (1.4 ± 1.9 days, $p < 0.001$).

## Influence of AKI on transplant patient outcomes (Table 4)

Mortality censored at 4 years was significantly higher in the AKI cohort compared to those who did not have an AKI episode during the study period ($p < 0.0001$, Fig. 2a). Overall mortality for the non AKI cohort was 8.4% compared to

**Table 4** Comparison of outcomes AKI vs No AKI in renal transplantation

| | AKI | No AKI | p value |
|---|---|---|---|
| Number of patients | 440 | 771 | |
| Mean duration of follow up since Transplant ± SD (days) | 3669.6 ± 2701.7 | 3515.7 ± 2780.3 | p = 0.34 |
| Overall mortality, % (n) | 34.8 (153) | 8.6 (66) | p < 0.001 |
| Patient status at end of study | | | |
| Living with functioning graft | 50.2 (221) | 91.6 (706) | p < 0.001 |
| Living with non-functioning graft | 15.0 (66) | 1.6 (12) | p < 0.001 |
| Died with functioning graft | 30.0 (132) | 8.3 (64) | p < 0.001 |
| Died with non-functioning graft | 4.8 (21) | 0.3 (2) | p < 0.001 |
| Renal function at end of study | | | |
| Creatinine mmol/l (mean ± SD) | 167.6 ± 82.4 | 123.8 ± 50.7 | p < 0.001 |
| eGFR (ml/min) (mean ± SD) | 42.3 ± 20.7 | 53.9 ± 17.3 | p < 0.001 |
| % with significantly worse renal function | 57 | 24.5 | p < 0.001 |

927 patients were included in analysis of the renal function at the end of the study variable (AKI, 221; No AKI, 706)

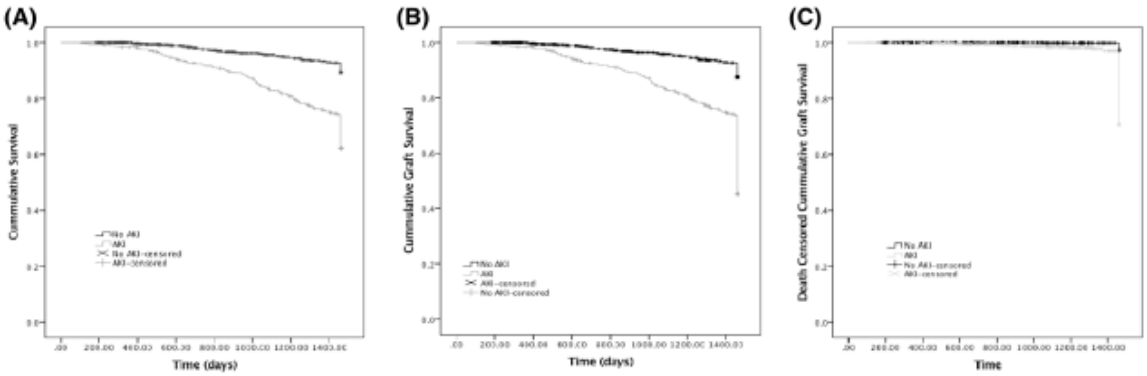


**Fig. 2** Impact of AKI on patient and graft survival. **a** 4 year censored survival of renal transplant patients experiencing at least one AKI episode compared to renal transplant recipients with no episodes of AKI during the study period. Renal graft survival (**b**) and death censored renal graft survival, both censored at 4 years, in patients experiencing at least one AKI episode compared to renal transplant recipients with no episodes of AKI during the study period

34.8% in the AKI group (RR 4.1, 95% CI 3.1–5.3, p < 0.001 compared to AKI cohort).

A comparison of the status of the patients at the end of the study period demonstrated significantly fewer patients alive with a functioning graft in the AKI group. More patients were alive with a non-functioning graft, and a higher proportion of patients had died, either with a functioning graft or with a non-functioning graft, in the AKI group. The association between AKI and graft failure was analysed by Kaplan–Meier estimation. Graft survival (GS), and death censored graft survival (DCGS) censored at 4 years, in the AKI cohort were significantly lower than in the non AKI group (p < 0.0001 for both GS and DCGS, Fig. 2b and c).

For patients who had poststudy renal function data available (i.e. alive with a functioning graft) the pre-study baseline renal function was no different in the AKI group compared to the non-AKI group (133.4 ± 52.0 µmol/l vs. 123.9 ± 17.3 µmol/l). In contrast, post-study serum creatinine was significantly higher in the AKI cohort compared to the non-AKI cohort (167.6 ± 82.4 µmol/l vs. 123.8 ± 50.7 µmol/l, p < 0.001). Similarly, whilst the eGFR was not significantly different at the beginning of the study (50.5 ± 18.1 ml/min for the AKI cohort vs. 53.9 ± 17.3 ml/min for the non-AKI cohort), at the end of the study period those from the AKI cohort had a significantly lower eGFR compared to the non-AKI group (42.3 ± 20.7 ml/min vs. 55.4 ± 20.1 ml/ml, p < 0.001). The percentage of patients with an end of study period renal function which was worse than the starting renal function as defined by a greater than 15% or 5 ml/min deterioration in eGFR,

was also higher in the AKI group (57.0% vs. 24.5%, RR 2.3 95% CI 1.9–2.7, $p < 0.001$). The duration of follow up from the time of transplant was no different between these two groups ($3669.6 \pm 2701.7$ days for the AKI group vs. $3515.7 \pm 2780$ days for the non-AKI group, $p = 0.34$).

## Discussion

Studies on AKI in renal transplant recipients are scarce but report a 40–50 fold higher incidence than the general population [11, 13], and occurring in up to 85% of hospitalised renal transplant patients [14]. It is postulated that the nature of AKI in renal transplants may be different to that seen in the general population with different susceptibilities related to denervated kidneys, susceptibility to haemodynamic instability, use of nephrotoxic drugs, especially calcineurin inhibitors, immune-related injury and predisposition to opportunistic infections. Whilst numerous published studies have described acute renal dysfunction in the immediate post-transplant phase [15, 18–22], very little is known of the nature and impact of AKI in the "maintenance" phase of renal transplantation. To address this, our focus was on AKI beyond the first 90 days of transplantation and well into the maintenance phase of prevalent renal transplant patients.

Our data report an incidence of AKI of 35%. In contrast, Mehrota et al. reported an AKI incidence of 11.3% in transplant patients in a study confined to hospitalised patients only, and identified AKI using coding data [11]. Our higher incidence may in part be explained by the high incidence of non-hospitalised AKI in renal transplant patients that we have identified but not previously reported. In contrast, a 51% incidence rate of transplant-associated AKI was reported by Nagarajan et al. [12]. That study focused on a relatively short term period of follow up, with AKI occurring predominantly in the first year of the follow up period. This higher reported incidence may therefore reflect the greater burden of AKI in the early phase following transplantation compared to our data which are of AKI occurring later in the phase of the prevalent transplant population. Nakamura et al., in contrast, reported an AKI incidence of 20.4% in transplant recipients, which is significantly less than our reported incidence. In this study, with a mean follow up period of four years post-transplantation, the majority of the AKI occurred within two years of the transplant [13], and AKI was only identified through nephrology/transplant clinics. Our non-selective approach, which identified all AKI based on every blood test that a prevalent renal patient had at any location, highlights that such an approach will significantly underestimate the true incidence of transplant-associated AKI.

In terms of clinical outcome, whilst AKI in the context of renal transplant carries a significant short term (30-day) and longer term mortality, this is similar to our previously reported data in the adult population [7, 23, 24], suggesting there is no excess in mortality when AKI occurs in renal transplant recipients compared to the general population. Our data also demonstrate that poor renal function prior to an AKI episode is associated with higher mortality. Although renal function in the immediate period following the AKI episode recovered in three-quarters of cases, AKI impacted negatively on graft survival and function, with a higher rate of graft loss, and significantly worse renal function in surviving patients in the AKI cohort. This is consistent with the previously published hospital-based, single centre and relatively small studies suggesting an association between AKI and risk of transplant loss [11–14]. Although the mechanistic link between AKI and graft loss remains speculative, it has been proposed that an episode of AKI may up-regulate inflammatory and fibrotic signalling pathways, leading to progressive structural kidney damage [25–28].

The only demographic differences between our AKI and non-AKI cohort was a higher prevalence of diabetic nephropathy as the cause of ESRF, and a higher serum creatinine at baseline. This is similar to the findings of the studies by Nakamura et al. [13] and Mehrotra et al. [11] demonstrating an association between post-transplant AKI, renal function and diabetes. For the general population, both diabetes [29–32] and CKD [33, 34] have previously been described in the literature as risk factors for AKI. In this context at least, our data would suggest the transplant population is therefore similar to the general adult population in terms of AKI risk. The higher baseline SCr in the AKI cohort along with the fact that patients with AKI had a conceivably higher prevalence of chronic graft dysfunction and a higher prevalence of the related alloimmune and non-alloimmune causes of chronic graft dysfunction suggest AKI may represent more a marker of clinical frailty rather than playing a direct pathogenetic role towards the risk of death and graft failure. It is of note that the prevalence of a kidney from a deceased donor was higher in our AKI cohort. This is consistent with previous published data highlighting deceased donor transplant to be a significant risk factor for the development of AKI [12]. This may be related to the incidence of delayed graft function and resultant renal impairment in this cohort, although this remains speculative as we were unable to report on delayed graft function in our study.

In the non-transplant population, in the majority of cases, AKI does not reflect intrinsic kidney disease but is rather a complication of other primary illnesses. Our data suggest that this is also reflected in transplant patients. In this study AKI in the context of the maintenance phase of renal transplant does not represent either rejection or recurrence of the primary renal disease. The majority of cases are associated with a clinical diagnosis of sepsis, with roughly a half identified via a non-nephrology/transplant request. This is

consistent with the work of Nakamura et al. demonstrating that bacterial infections and predominantly urinary tract infections were the most common aetiological factors contributing to renal-transplant-associated AKI, although this study was confined to a small number of living donor recipients alone and in the setting of the outpatient nephrology/transplant clinic [13]. This pattern of AKI is however different to that reported in the early post operative period when the nephrotoxic effect of immunosuppressive agents, in particular calcineurin inhibitors and rejection, are more common [15].

Our data demonstrate that over half of transplant-associated AKI is detected in the community, with only a small minority of cases being admitted to hospital. These cases therefore would not be reported in studies based on hospitalisation, nor would AKI identified through hospital coding. Although HA-AKI in this study represents roughly a third of the AKI cases, it should be noted that there were also a significant number of episodes classified as 'undetermined in hospital alerts', as these patients, whilst alerting in an inpatient setting, had no results for the previous 7 days. Our data therefore likely reflect a significant underestimation of the true incidence of HA-AKI in renal transplant recipients. Mortality following HA-AKI in this transplant cohort was significantly higher than following CA-AKI. This higher mortality is not a reflection of AKI severity per se, as there was a higher proportion of incident AKI stage 3 alerts in the CA-AKI group. The higher mortality in the HA-AKI cohort again mirrors our previous data in the general adult and paediatric populations [9, 35]. As the majority of AKI cases do not represent intrinsic kidney disease it is likely that the excess mortality in HA-AKI reflects the severity of the primary illness precipitating AKI. Previously we have demonstrated that in the general adult and paediatric populations, in those surviving an AKI episode, renal function is better following HA- compared to CA-AKI [7–9, 16]. In part at least this reflects clinical inactivity and a failure to recognise the importance of the alert. This was supported by the lower number of patients with CA-AKI compared to HA-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. It is of note that few patients in the transplant cohort did not have any follow-up bloods, however, as in the general non-transplant adult population, in this study of transplant patients the time to repeat a measure of renal function was significantly longer in the CA-AKI group which may reflect a slower response time that may then in turn result in later initiation of interventions which may facilitate recovery of renal function.

Although this study is to our knowledge the first national study using an e-alert-based system to characterise the magnitude and impact of AKI in renal transplant recipients, its findings need to be qualified by its limitations. As the e-alert system is IT driven it lacks "intelligence" and therefore there is no clinical context applied. Using an IT-based approach also excludes patient clinical information, such as patient co-morbidities, medication. Linkage to comorbidity data in particular would have helped strengthen the suggestion made by this study that AKI may represent more a marker of clinical frailty rather than playing a direct pathogenetic role towards the risk of death and graft failure. We are also unable to generate linkage to primary care data sets. As a consequence, a detailed analysis of the clinical response to the AKI episode cannot be captured. Our data also lack details on the need for RRT, and do not shed light on the cause of death. Our data report the incidence of AKI in which the diagnosis is a creatinine-based definition in which the baseline creatinine is generated by the patients' historical results. As such, this may not meet the strict agreed AKI definition of "abrupt deterioration", and does not take into account a "urine output"-based AKI diagnosis. Despite these limitations our study provides a detailed characterisation of AKI in renal transplant recipients and highlights its impact on patient and graft survival.

**Author contributions** AJ and JH designed the study, collected and analysed the data and produced the figures. JDW, KD, MS 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.

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**Availability of data** The data that support the findings of this study are available on request from the corresponding author.

## Compliance with ethical standards

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical approval** The study was approved under the terms of Service Evaluation Project Registration.

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**Appendix 3.6:** Published work 6 related to this thesis:

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Original paper

ORIGINAL PAPER

# The influence of socioeconomic status on presentation and outcome of acute kidney injury

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## Summary

**Aim:** Although socioeconomic background is known to impact on the incidence and progression of chronic kidney disease, its influence of on the presentation and outcome for acute kidney injury is not known and is the subject of this study.
**Design:** The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients >18 years of age between March 2015 and November 2017.
**Methods:** Socioeconomic classification of patients was derived from the Welsh Index Multiple Deprivation score (WIMD). Patients were grouped according to the WIMD score by their postcode, and the ranked data were categorized into percentiles and correlated with incidence and measures of AKI severity and outcome.
**Results:** Date was collected on a total of 57 654 patients. Increased deprivation was associated with higher AKI incidence rates, more episodes of AKI per patient and more severe AKI at presentation. In contrast 90-day mortality was highest in the most affluent areas. Mortality in affluent areas was driven by increased patient age. Corrected for age 90-day mortality was higher in areas of increased deprivation.
**Conclusion:** This study highlights that AKI incidence presentation and outcomes are adversely affected by social deprivation. Further studies are required to understand the extent to which these differences reflect patient related factors or regional differences in provision and access to care.

## Introduction

Acute Kidney Injury (AKI) is characterized by a sudden decline in renal function which is associated with increased patient morbidity and mortality.[1] In patients surviving an acute episode, AKI is also associated with longer term effect on patient's health as there is an increase in incidence of subsequent Chronic Kidney disease and a higher mortality than in patients who have not experienced AKI.[2] The increasing incidence of AKI is well documented. Furthermore, a recent study of AKI in Wales suggest that there is an association between the incidence of AKI and measures of social deprivation. With a higher incidence of AKI in those from socially deprived areas.[3]

The relationship between Socioeconomic deprivation and higher mortality and reduced life expectancy in the UK are well established.[4] A higher incidence and worse clinical outcomes related to social deprivation have been described for a number

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of medical conditions including coronary heart disease[5,6] and the most common forms of cancer.[7–10]

In Renal Medicine the relationship between socioeconomic deprivation, severity of chronic kidney disease (CKD) and poor clinical outcomes is well documented,[11–16] as are the effects of social deprivation in renal transplantation.[17–19] Whilst some aspects of the impact of social deprivation on renal disease have therefore been described, its impact on the incidence and severity of AKI at presentation and outcome following AKI has not been previously reported. This study aims to describe the relationship between social deprivation and the severity of AKI at presentation and clinical measures of outcome.

## Materials and methods

### Setting

Data was collected from the seven health boards in the National Health Service in wales, representing a population of 3.06 million people. The Medical Record Number (MRN) was used as the patient identifier. This unique reference number is allocated to patients registered in the National Laboratory Information Management System (LIMS) which therefore allows for multiple visits/blood test requests to be linked. The study has been approved under the conditions of 'Service Evaluation Project Registration'.

### The electronic AKI reporting system

The Welsh electronic reporting system generates an AKI alert by comparing a current creatinine value to historic creatinine measurements for the same patient in real time. It defines AKI according to KDGIO increase in creatinine parameters.[3] Patients who have an AKI episode but no previous recorded creatinine values will not be alerted by this system.

### Data collection

Data was collected on all individuals over the age of 18 years old for which an AKI alert was generated in any location across Wales between March 2015 and November 2017. Patients receiving renal replacement therapy and patients with a known renal transplant, and AKI alerts generated on the renal tertiary center base ward were excluded from the analysis to avoid spurious labelling of AKI resulting from fluctuations in serum creatinine related to renal replacement therapy as previously described.[3] An incident AKI episode was defined as 30 days, and the first AKI alert was defined as the incident alert (i.e. any AKI e-alert for the same patient within 30 days of the incident alert was not considered a new episode).

In addition to measurements of renal function data was collected on patient age, gender, stage of AKI, pre-existing CKD [(eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration eGFR equation[20]) <60 ml/min per 1.73 m2 derived from the baseline SCr] and the clinical location at which the alert was generated.

All patients for which the first alert was issued during a hospital admission who also had a normal SCr value generated in a hospital setting within the preceding 7 days were defined as Hospital acquired (HA)-AKI. Conversely patients who had an alert in a setting outside of hospital were defined as having Community acquired AKI (CA-AKI). For the CA-AKI, when the follow up measurement (first or second measurement) of renal function was in a hospital setting the patient was defined as hospitalized CA-AKI.

Progression of AKI (defined as a peak AKI stage higher that the incident AKI stage or for stage 3 alerts an increase $\geq 50\%$ from the SCr generating the alert), renal function at 90 days and patient mortality at 90 days were collected as measures of clinical course and impact of AKI. Non-recovery of renal function was defined as a serum creatinine level at 90 days, which remained above the serum creatinine baseline which remained consistent with a definition of AKI.

The day on which the incident AKI alert was generated was also recorded in order to generate two patient groups: those generating an AKI at the weekend and those generating an alert on a weekday.

Contact with medical services prior to the AKI episode was determined by recent measurement of renal function defined as a measurement of renal function within the preceding 30 days of the incident AKI alert.

Incidence rate was calculated using Mid-2013 Office for National Statistics (ONS) Population Estimates and patient level postcode analyses.[21] Data on patient mortality were collected from the Welsh Demographic Service.[22] Socioeconomic classification of patients was derived from the Welsh Index Multiple Deprivation score (WIMD). This is the Welsh Government's official measure of relative deprivation in which the population of Wales is divided into 1909 geographical units called lower super output areas (LSOAs) each with an average population of 1600 people.[23] The WIMD score is constructed from a weighted sum of the deprivation score for each of the following domains: Income (23.5%), Employment (23.5%), Health (14.0%), Education (14.0%), Access to Services (10.0%), Community Safety (5.0%), Physical Environment (5.0%) and Housing (5.0%). Patients were grouped according to the WIMD score by their postcode and corresponding LSOA of residence, and the ranked data were categorized into percentiles, with percentile 1 being the most socio-economically deprived and percentile 100 being the least deprived.

Statistical analysis was carried out using SPSS software, version 20 (IBM SPSS, Chicago, I); Pearsons Coefficient was calculated to determine correlation between measures of social deprivation of AKI readouts. Multi-variate Cox proportional hazard modeling was used to analyse patient survival. P values $<0.05$ were considered statistically significant.

## Results

### Incidence and demographics

A total of 57 654 patients triggered and electronic AKI alert between March 2015 and 2017. In total there were incident alerts equating to an average of 1.45 AKI episodes per patient. The incidence of AKI during this time period was 4.1 patients per 1000 population per year. The average age of the patient was $71.05 \pm 17.0$ years. Overall 90-day mortality for the whole cohort was 25.8%. The majority (78.47%) of episodes were classified as AKI stage 1 at presentation, with 14.5% classified as AKI stage 2 and 7.03% classified as AKI stage 3; 30.4% of patients had pre-existing CKD. Patients of 49.8% and 38.5% first presented with CA-AKI and HA-AKI, respectively. Patients of 11.7% whilst alerting in an in-patient setting had no results for the previous 7 days, and therefore could not be confidently designated as either CA- or HA-AKI definitions, and excluded from the sub-group analysis.

### Relationship between socioeconomic status and presentation

The relationship between incidence of AKI and patient socioeconomic status is shown in Figure 1. There was a strong

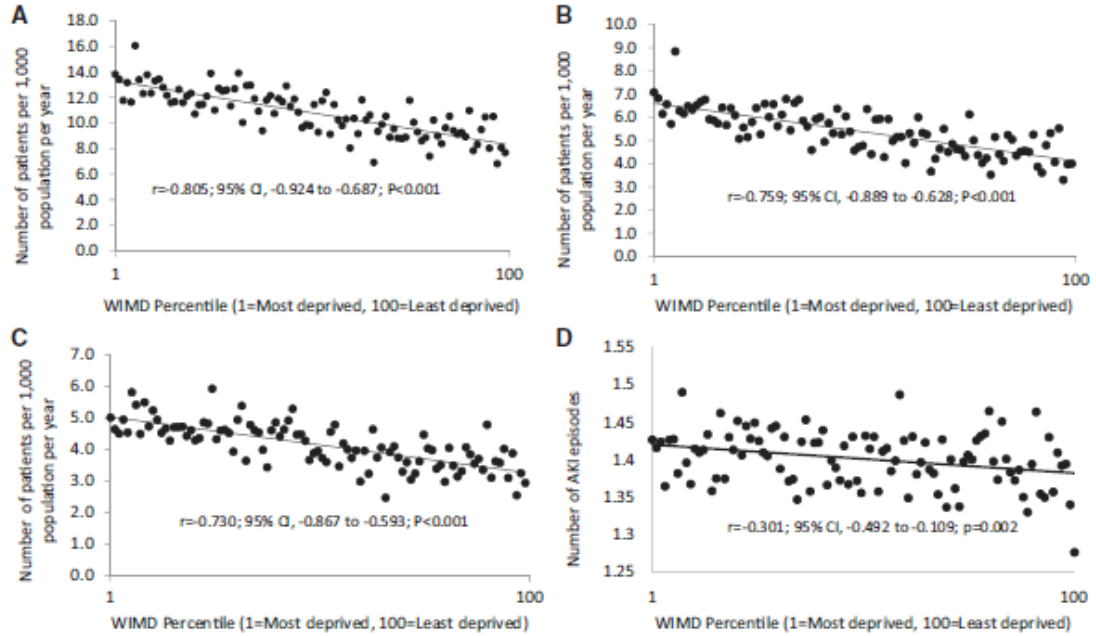


**Figure 1.** The relationship between the incidence of AKI and social deprivations as measured by WIMD percentile. (A) Total AKI incidence rate. (B) Incidence of Community acquired AKI. (C) Incidence of Hospital acquired AKI. (D) Average number of AKI episodes per patient during the study period. WIMD, Welsh Index of Multiple Deprivation, where percentile 1 is the most deprived and percentile 100 is the least deprived.

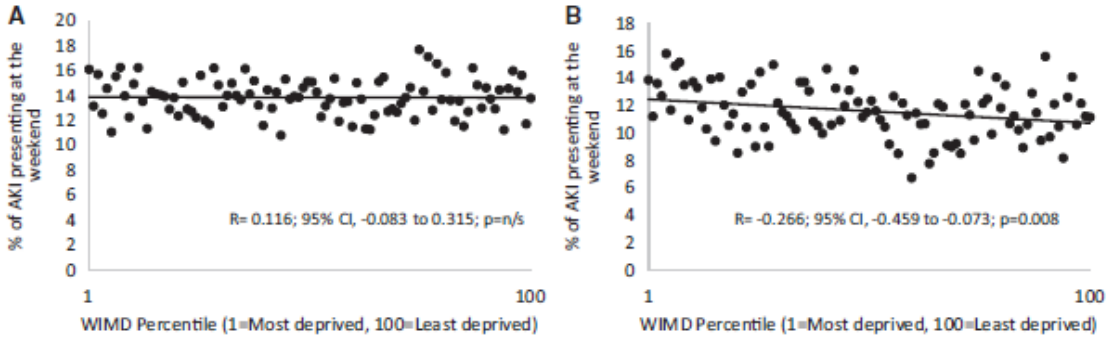


**Figure 2.** Correlation of Percentage of total AKI (A) or community acquired AKI (B) generating an electronic AKI alert on a weekend (Saturday and Sunday) and patient socioeconomic status as assessed by WIMD percentile.

negative correlation between ranking by WIMD score and the incidence of AKI ($r = -0.805$; 95% CI, –0.924 to –0.687; $P < 0.001$). There was also a negative association between the number of AKI episodes per patient and socioeconomic measures ($r = -0.301$; 95% CI, –0.492 to –0.109; $P = 0.002$; Figure 1D). The negative correlation between ranking by WIMD and AKI incidence also seen in sub-group analysis of CA- ($R = -0.759$; 95% CI, –0.889 to –0.628; $P < 0.001$) and HA-AKI ($R = -0.730$; 95% CI, –0.867 to –0.593; $P < 0.001$). Although weekend presentation to hospital has previously been reported to be associated with social deprivation, whilst there was no relationship between the day of diagnosis of AKI and socio-economic measures in the whole cohort ($R = 0.116$; 95% CI, –0.083–0.315; $p = n/s$: Figure 2A), there was a negative correlation between weekend detection and socioeconomic deprivation in the CA-AKI sub-group ($R = -0.266$; 95% CI, –0.459 to –0.073; $P = 0.008$; Figure 2B).

## Mortality and socioeconomic status

The relationship between socioeconomic measures and 90-day mortality following AKI is shown in Figure 3. In contrast to the relationship between incidence of socio-economic deprivation, there was a strong positive correlation between ranking by WIMD score and the 90-day mortality with a higher proportion of AKI patients dying within 90 days of presentation in the most socially affluent areas ($R = 0.312$; 95% CI, 0.122–0.503; $P = 0.002$). This positive relationship between mortality and socio-economic measures was seen in both CA-AKI and HA-AKI (Figure 3B and C).

Kaplan–Meier survival curves by WIMD quartile are shown in Figure 4, with Quartile 1 representing the most socially deprived and Quartile 4 the most affluent geographical areas. Mean survival was longest in the most deprived WIMD quartile (475.5 days, 95% CI 471.1–479.8) and fell progressively in each WIMD quartile

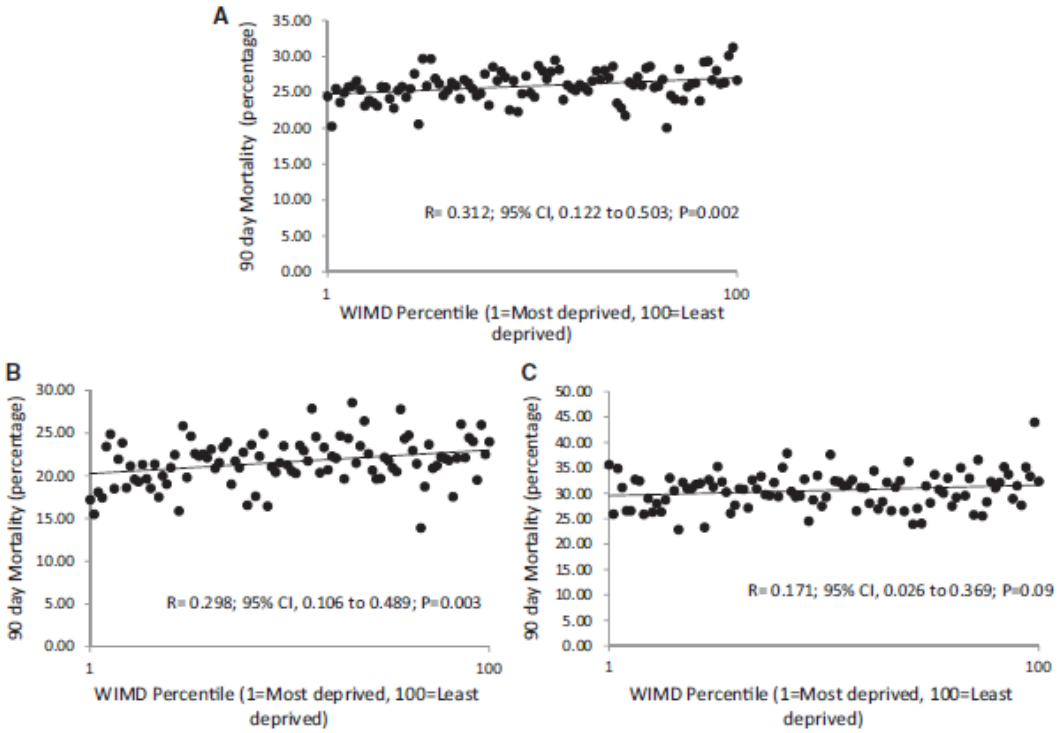


Figure 3. Correlation of percentage of patients who died within 90-day of all incident AKI patients (A), incident community acquired AKI patients (B) or incident hospital acquired AKI patients (C). Community acquired AKI includes a total of 41 731 patients, Hospital acquired AKI includes a total of 32 692 patients.

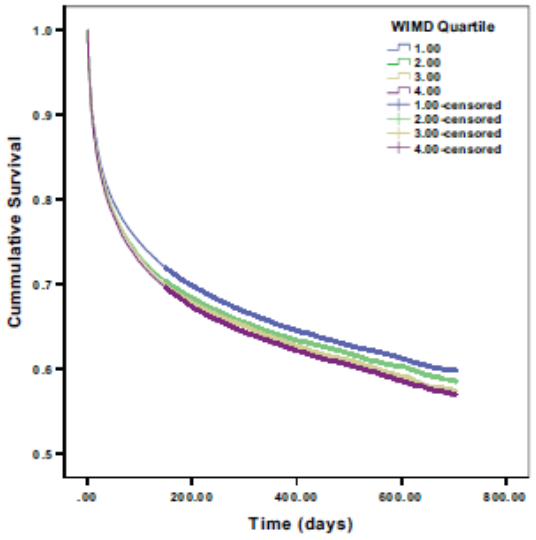


Figure 4. Kaplan–Meier survival curves for AKI patients stratified by WIMD quartile. Quartile 1 represents the most deprived and quartile 4 the most affluent ranked geographical areas. Data was censored at 2 years.

representing increasing affluence (2nd quartile 467.1 days, 95%CI 463.0–471.3, 3rd quartile 462.9 days, 95% CI 458.5–467.2, 4th quartile 459.3 days, 95% CI 454.4–463.9, $Chi^2$ 31.64, P< 0.0001).

## AKI severity and socioeconomic status

Severity of AKI at presentation was determined by the % of patients with AKI stage 2 or 3 at presentation and also by the proportion of patients who progressed to a higher AKI stage following initial diagnosis (Figure 5). There was a weak negative correlation between ranking by WIMD score and the severity at presentation. This was true when assessing severity as either the percentage of patients presenting with AKI stage 3 (R = –0.201; 95% CI, –0.398 to –0.005; P = 0.045) or the combined percentage presenting with AKI2 and 3 (R = –0.217; 95% CI, –0.413 to –0.022; P = 0.03). This relationship held true for CA-AKI (Figure 5B) but not for HA-AKI (Figure 5C). In contrast severity of disease as assessed by progression of AKI to a higher stage was not significantly related to measures of social deprivation (Figure 5D).

## Patient demographics

The relationship between age at presentation of AKI and patient socioeconomic status is shown in Figure 6. There was a strong positive correlation between ranking by WIMD score and the age of patients presenting with AKI (R = 0.876; 95% CI, 0.780–0.973; P < 0.001: Figure 6A). This strong positive relationship was also seen in both the CA-AKI (R = 0.855; 95% CI, 0.751–0.959; P < 0.001; Figure 6B) and HA-AKI (R = 0.807; 95% CI, 0.689–0.926; P < 0.001: Figure 6C).

Cox regression proportional hazard modeling analysis was used to assess corrected patient mortality. For the whole cohort higher hazard of death was associated with older age (HR, 1.037; 95% CI, 1.036–1.38; P < 0.001) and a higher WIMD ranking (i.e. less social deprivation) (HR, 1.001; 95% CI, 1.001–1.002; P < 0.001).

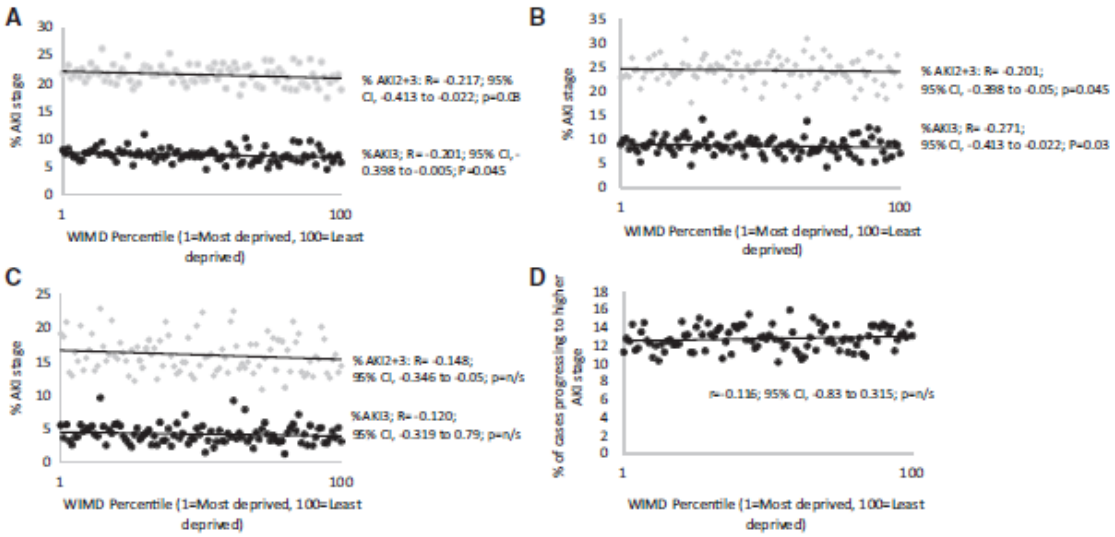


Figure 5. Correlation of measures of AKI severity at presentation and socioeconomic status. Severity of AKI as assessed by the percentage presenting with AKI 3 or the combined percentage presenting with AKI stage 2 and 3, of all patients (A), patients with community acquired AKI (B), hospital acquired AKI (C) and social deprivation. Severity of AKI was also determined by the percentage of patients who progressed to a higher AKI stage, defined as a peak AKI stage higher that the incident AKI stage or for stage 3 alerts an increase ≥ 50% from the SCr generating the alert (C).

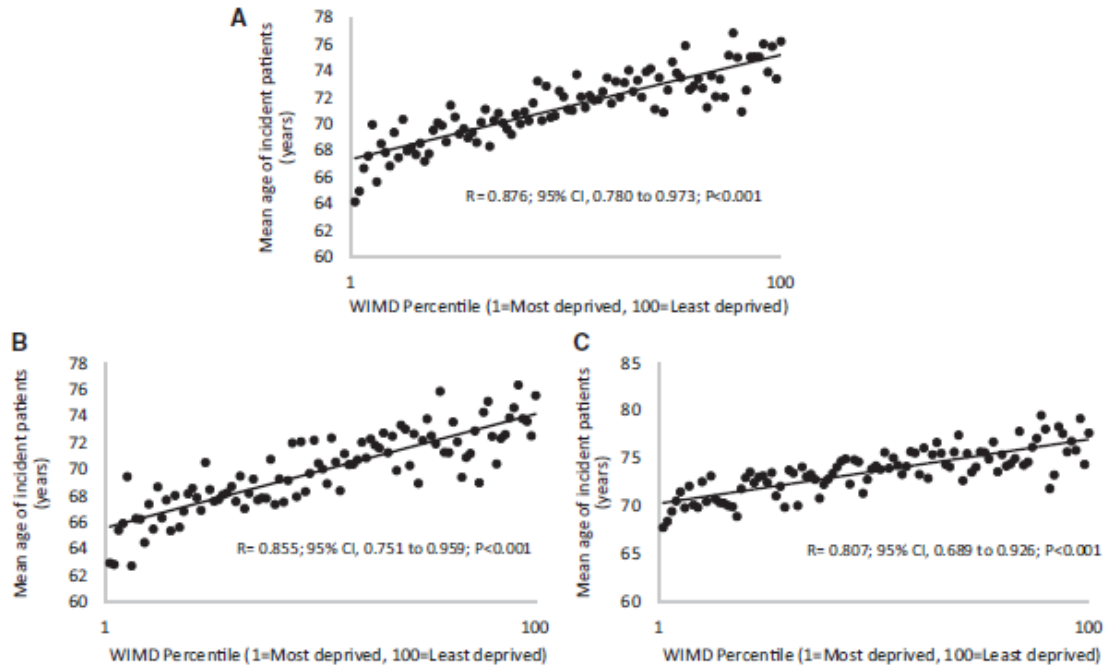


Figure 6. Correlation of age of all incident patients (A), patients with community acquired AKI (B) and hospital acquired AKI (C) at presentation and socioeconomic status measured by WIMD percentile.

Adjusted for age however the HR of death was lower in patients with higher WIMD ranking (adjusted HR, 0.999; 95% CI, 0.998–0.999; P < 0.001).

Kaplan–Meier survival curves for patients aged <65 years of age and ≥65 years of age by WIMD quartile are shown in Figure 7, with Quartile 1 representing the most socially deprived and Quartile 4 the most affluent geographical. For the patients aged <65 years there was no effect of social deprivation and mean survival. Mean survival was no different between the highest and lowest WIMD quartiles (WIMD Quartile: 1 577.9 days 95%CI 574.4–585.6, Quartile 4: 579.5 95%CI 575.2–581.8, Chi$^2$ 5.03, P = 0.169). For older patients, aged ≥65 year at the time of the AKI episode, mean survival was significantly shorter in the most deprived WIMD quartiles (Mean survival; Quartile 1:

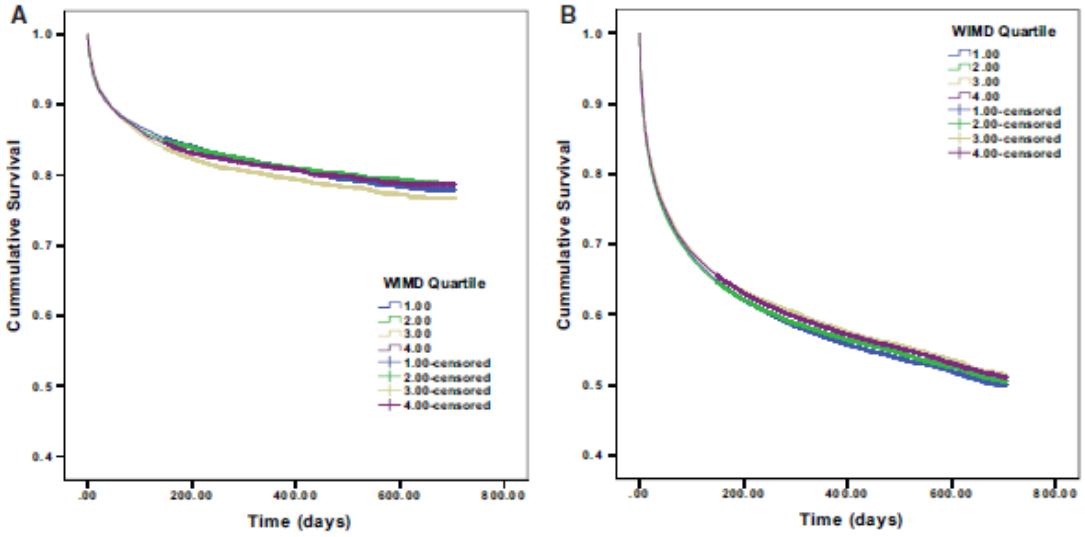


Figure 7. Kaplan–Meier survival curves for for patients aged <65 years (A) of age and ≥65 years of age (B) stratified by WIMD quartile. Quartile 1 represents the most deprived and quartile 4 the most affluent ranked geographical areas. Data was censored at 2 years.

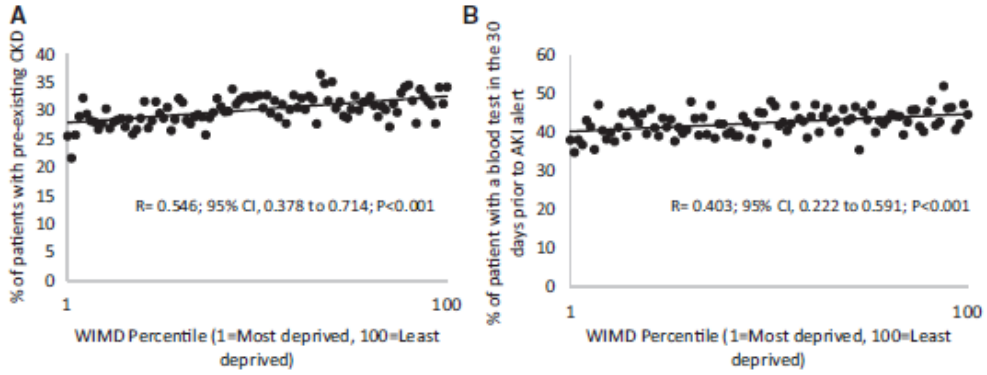


Figure 8. Correlation between the percentage of AKI patients with pre-existing Chronic Kidney Disease (A) and previous measure of renal function in the month prior to presentation of CA-AKI (B) and WIMD ranking.

419.0 days, 95%CI 413.8–424.2; Quartile 2: 412.3 days, 95%CI 416.3–426.4, Quartile 3: 428.9 days, 95%CI 423.8–434.1, Quartile 4: 426.7 days 95%CI 421.3–432.1, $Chi^2$ 9.05, $P = 0.029$).

Pre-existing CKD was used as a surrogate marker of co-existing co-morbidities (Figure 8A). There was a positive correlation seen between the proportion of AKI patients with pre-existing CKD and WIMD ranking. ($R = 0.546$; 95% CI, 0.378–0.714; $P < 0.001$). A previous measure of renal function in the month prior to presentation of CA-AKI was used as a surrogate marker of recent medical contact again reflecting likely co-existing co-morbidity (Figure 8B). There was also a significant positive association between prior measurement of renal function and WIMD ranking ($R = 0.403$; 95% CI, 0.222–0.591; $P < 0.001$).

## Discussion

The striking finding of this study is that despite the incidence of AKI being lower in the more affluent areas, mortality is higher. This excess in mortality is not explained by the severity at presentation as AKI at presentation is more severe in the socially deprived areas and tend to be milder in the more affluent cohort. The data however suggest that excess AKI related mortality in affluent areas is related to the older age of the patients in the affluent areas presenting with AKI.

It is well recognized that we have an ageing population, which reflects the benefit of efforts to improve population health. Despite this, an aging population does bring additional challenges, a key one of which is frailty. Frailty is a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves. Around 10% of people aged over 65 years have frailty, rising to between a quarter and a half of those aged over 85 years. Our data suggest that the mortality in AKI in affluent areas may provide another measure of frailty in the aging population. Previous data defining the epidemiology of AKI in Wales demonstrated increased higher hazards of death associated with older age.[3] The current

data reflects this in that the AKI associated mortality in the affluent areas is a reflection of increased life expectancy and an aging population. In order to reduce AKI associated mortality in this patient group, clinicians need to understand the significance of small changes in serum creatinine particularly in an elderly population. Clinicians responding to an electronic AKI alert, should be encouraged to undertake early clinical assessment of acute illness and volume status, prompt review of medications with temporary cessation of nephrotoxic medications where appropriate.

Our linear regression analysis also demonstrates that once corrected for age, there is a higher likelihood of death in the areas of social deprivation, most pronounced in the older patient group as shown in the Kaplan–Meier survival data in the older patient group. This needs to be quailed by the finding that the effect of age on survival was not liners for each WIMD quartile as survival in the second quartile was shorter that the first and most deprived quartile. The association between social deprivation and increase mortality is well described. Data from Wales which includes some of the poorer areas in Europe, demonstrate fundamental inequalities between the poorest and wealthiest.[24] Men from poorer areas of Wales die 8.8 years earlier and women 7.2 years earlier than their wealthier neighbors. This is associated with a higher incidence of smoking, obesity, poor diet, inactivity and alcohol consumption.[25–27] These are risk factors are aetiologically linked to the four diseases that account for 64% of early deaths; cancer, heart disease, stroke and diabetes. As a result, the difference the 'healthy life expectancy' within Wales is 18.7 years for men and 18.2 years for women in the least affluent areas. This suggests that socioeconomic deprivation is associated with 'pre-mature ageing'. Previous studies based in South Wales have demonstrated that age and pre-existing CKD are the most useful variables which can be used to predict the likelihood of developing AKI.[28] Given the evidence suggesting pre-mature aging in the socially deprived cohort what we consider to be 'old' may need to be redefined and it is not simply a question of 'years'. In this study correction for age in a linear regression model also demonstrates inequality of outcome. In the socially deprived areas the weight of all 'early onset' of chronic conditions such as cardiovascular disease, diabetes and obesity leads to a poorer outcome for AKI in the poorer areas, suggesting that mortality in AKI in socially deprived areas reflects the increased burden of co-morbidity. The burden of co-morbidity and poor outcome has also been described in other aspects of nephrology, with social deprivation being associated with poor outcome in CKD, with higher rates of progression of CKD and also poor outcomes once on dialysis.[11–13] Outcome following renal transplantation also follows the same pattern with a higher rate of post-operative complications and poorer outcomes associated with social deprivation.[17] This is also consistent with the literature related to cardiovascular disease where it is recognized that socio-economic deprivation is a marker of poor outcome following coronary artery disease. Patients undergoing coronary artery bypass grafting from socially deprived areas tend to be younger, have more risk factors and as a result have a worse outcome post-operatively due to increased risk of complications.[5,6] Most chronic diseases are preventable and adopting four of five 'healthy behaviors' such as increasing exercise, reducing smoking and alcohol intake and modification of diet, have been shown to impact on the rates of diabetes vascular disease and cancers.[29] The challenge is therefore to educate and support patients to make positive changes to lifestyles to reduce the burden of co-morbidities and improve life expectancy in socially deprived areas.

What else can we do to improve clinical outcomes related to social inequalities? In addition to the impact of co-morbidity, poor medical outcomes associated with social deprivation have been ascribed with inequality of access to specialist services. Specifically access to specialist cardiology services has also been shown to be reduced in the socioeconomically deprived cohort which contributes to poor outcome.[30] Access to specialist services have also been demonstrated to influence outcome in nephrology, with patients from socially deprived less likely to receive access transplant waiting lists and be considered for living related a kidney transplantation.[18,19] Recent data generated in Wales suggest that access to medical services also affects AKI outcomes. Almost half of people that present with Community acquired AKI have a measure of renal function in the month prior to the AKI episode demonstrating that they are already known to medical services. This suggest that for some patient AKI may be predictable and potentially be avoided.[31] Poor outcome for CA-AKI in primary care has also been associated with lack of early recognition, work which has led to the recommendation that a clinical review and repeat measurement of renal function should be undertaken within 7 days for all patients with an AKI electronic alert in primary care.[32] Poor outcome for AKI has also been described for patients in whom AKI is detected at the weekend, and effect related to reduced admission rates and access to hospital in-patient care during weekends.[33] Although there is data to support an effect of social deprivation on access to hospital services at the weekend,[34,35] no previous work has described the effect of social deprivation on AKI weekend presentation and outcome. Previous studies suggest that CA-AKI detected on the weekend is associated with a worse outcome.[33] In the current study, a higher proportion of CA-AKI was detected at the weekend in socially deprived areas, a factor therefore likely to influence mortality following AKI in socially deprived regions.

Although this study is to our knowledge the first national study to define the relationship between measures of social deprivation and AKI, its findings need to be qualified by its limitations. As the e-alert system is IT driven it lacks 'intelligence' and therefore there is no clinical context applied. Using an IT based approach 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, the need for RRT, and does not shed light on the cause of death. Similarly, this method of identification of AKI does not allow details on the date and time of admission to hospital, meaning the diagnosis of HA-AKI is dependent on a previous test of renal function requested from an in-patient setting. The study is also limited in that any patient presenting with AKI but without a measurement of renal function in the previous 365 days will not be included. Similarly, the reliance on a definition of AKI based on serial changes in serum creatinine does not take into account urine output based AKI diagnosis which may also lead failure to include all cases of AKI. Despite these limitation, our data suggest that in addition to lifestyle and modification of co-morbidities, the availability and accessibility of resources and services may impact on AKI outcome measures. Careful consideration is therefore needed in order to optimize resource planning to address caseload for clinician to reflect significant difference in workload which reflect the clinical needs of patients in deprived and affluent. It is therefore likely that to improve outcomes there is a need for both social and medical interventions and the needs of patients may be somewhat different in different geographical areas. In order to improve AKI outcomes further research is needed to identify key modifiable

targets for intervention which may address patients needs from different socio-economic backgrounds.

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DP analysed the data and produced the figures and wrote the report. JH and RD collected the data and wrote the report. JDW 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. 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.

*Conflict of interest*: None declared.

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**Appendix 3.7:** Published work 7 related to this thesis:

Holmes *et al*. (2019) 'Acute Kidney Injury, Age, and Socioeconomic Deprivation: Evaluation of a National Data Set', Kidney International Reports

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# Acute Kidney Injury, Age, and Socioeconomic Deprivation: Evaluation of a National Data Set

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**Introduction**: This study examined the relationship among age, measures of social deprivation, and incidence and outcome of acute kidney injury (AKI).

**Methods**: The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients 18 years or older between March 2015 and January 2017. Socioeconomic classification of patients was derived from the Welsh Index of Multiple Deprivation (WIMD). Patients were grouped according to their WIMD score, and Multivariate Cox proportional hazard modeling was used to adjust the data for age. The ranked data were categorized into percentiles and correlated with incidence, and measures of AKI severity and outcome.

**Results**: Analysis included 57,654 patients. For the whole cohort, the highest 90-day survival was associated with the most socially deprived cohorts. There was a significant negative relationship between age-adjusted incidence of AKI and the WIMD score. In patients 60 years or older, there was an inverse correlation between WIMD score and survival that was not evident in those younger than 60. AKI severity at presentation was worse in patients from areas of social deprivation. Social deprivation was associated with a significantly higher proportion of preexisting chronic kidney disease (CKD) in patients with AKI older than 60, but not in those younger than 60.

**Conclusion**: Overall mortality following AKI was higher in least-deprived areas, reflecting an older patient cohort. In contrast, social deprivation was associated with higher age-adjusted AKI incidence and age-adjusted mortality following AKI. The excess mortality observed in more deprived areas was associated with more severe AKI and a higher proportion of preexisting CKD.

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AKI, characterized by a sudden decline in renal function, is associated with increased patient morbidity and mortality.[1,2] Most publications of large series characterizing AKI rely on making and recording an accurate diagnosis of AKI through hospital coding or retrospective review of hospital records.[3–6] Based on a presumption that early identification may help raise standards of care and improve patient outcomes, an automated real-time electronic (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 England and Wales. Across Wales, an AKI alert is generated when the all Wales Laboratory Information Management System (Intersystems TrakCare Lab, Cambridge, MA) automatically compares measured serum creatinine values on an individual patient against previous results on the system database. Using the electronic AKI alert, we have developed a centralized data collection system to provide a comprehensive characterization of the incidence of AKI identified by an electronic alert, and its outcome in Wales.[7–9]

In renal medicine, the relationship between socioeconomic deprivation, severity of CKD, and poor clinical outcomes is well documented,[10–14] as are the effects

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of social deprivation in renal transplantation.[15–17] Much less is known regarding the relationship between social deprivation and AKI. We have previously demonstrated that the incidence of AKI is related to measures of social deprivation, with a higher incidence in the most disadvantaged areas.[7] In contrast, a higher mortality was seen in AKI in the most affluent areas.[18] We postulate that this discrepancy relates to a longer life expectancy in areas of affluence, which influences the nature of patients presenting with AKI. In the current study, we have further examined the relationship among age, measures of social deprivation, and incidence and outcome of AKI.

## METHODS

### Setting

Data were collected from all Health boards in the National Health Service in Wales, representing a population of 3.06 million people. The Medical Record Number, a unique reference number allocated to patients registered in the National Laboratory Information Management System, was used as the patient identifier. The study has been approved under the conditions of "Service Evaluation Project Registration."

### The Electronic AKI Reporting System

The AKI alert is generated by comparing a current creatinine value with historic creatinine measurements for the same patient in real time. It defines AKI according to Kidney Disease: Improving Global Outcomes increase in creatinine parameters.[7] Patients with no previous recorded creatinine values will not generate an alert. For patients with preexisting CKD, the algorithm will only generate alerts for acute or chronic AKI (i.e., only if a significant acute rise is detected).

### Data Collection

Data were collected on AKI alerts generated on all individuals older than 18 in any location across Wales between March 2015 and January 2017. To avoid spurious results resultant from fluctuations in creatinine related to renal replacement therapies, dialysis patients, patients with a known renal transplant, and AKI alerts generated on the renal tertiary center base ward were excluded from the analysis.[7] Patients were counted only once in the analysis (i.e., any alert for the same patient other than the first was excluded).

In addition to measurements of renal function, data were collected on patient age, gender, stage of AKI, preexisting CKD (estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate equation[19] and preexisting CKD was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 $m^2$ derived from the baseline serum creatinine), and the clinical location at which the alert was generated. All stages of AKI were included in the analysis; however, severity of AKI at presentation was determined by the percentage of patients presenting with AKI stages 2 and 3.

Incidence rates were calculated using mid-2013 Office for National Statistics population estimates and patient-level post code analyses.[20] Data on patient mortality at 90 days following each episode were collected from the Welsh Demographic Service.[21] Socioeconomic classification of patients was derived from the WIMD score.[22] The overall WIMD is a weighted area level aggregation of 8 domains of deprivation that can be recognized and measured separately (income, employment, education, health, geographical access to services, housing, and physical environment). Patients were grouped according to the WIMD score by their postcode and corresponding Lower-layer Super Output Area of residence, with results presented as ranked data. The ranked data were categorized into percentiles, with percentile 1 being the most socioeconomically deprived and percentile 100 being the least deprived.

Statistical analysis was carried out using SPSS software, version 20 (IBM SPSS, Chicago, IL). Pearson's coefficient was calculated to determine correlation between measures of social deprivation of AKI readouts. Multivariate Cox proportional hazard modeling was used to analyze patient survival. To exclude the influence of age on survival a Cox proportional hazards regression model was used to generate an age $\beta$ correction factor of 0.034 per year. This enabled the adjustment of each WIMD percentile population to age 60. $P$ values $<0.05$ were considered statistically significant.

## RESULTS

A total of 57,654 patients triggered an electronic AKI alert between March 2015 and January 2017. Overall 90-day mortality for the whole cohort was 25.8%.

### Survival, WIMD, and Age Distribution of AKI

The relationship between socioeconomic measures and 90-day survival following AKI is shown in Figure 1. There was a strong positive correlation between ranking by WIMD score and 90-day survival (Figure 1a), with a higher proportion of patients with AKI surviving at 90 days in the most socially deprived areas ($R = 0.312$; 95% confidence interval [CI]: $-0.503$ to $-0.122$; $P = 0.002$). In line with the hypothesis that reduced survival associated with AKI in affluent areas is a reflection of longer life expectancy in the most affluent areas, the percentage of patients with AKI who were 80 years or older

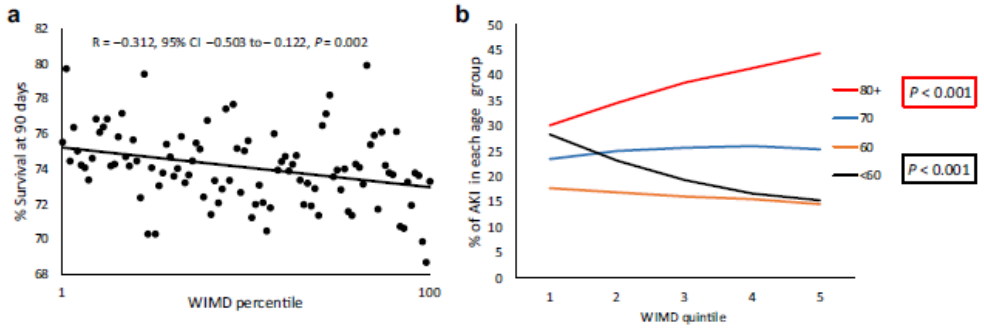


**Figure 1.** The relationship between 90-day survival (a), and age distribution (b) of patients with acute kidney injury (AKI) and social deprivation. For 90-day survival, social deprivation was measured by Welsh Index of Multiple Deprivation (WIMD) percentile, where percentile 1 is the most deprived and percentile 100 is the least deprived. For age distribution, the data represent percentage of patients in each category of social deprivation with AKI in each of the age groups <60 years, 60–69 years, 70–79 years, and ≥80 years with the social deprivation, expressed as WIMD quintiles with quintile 1 representing the most deprived and quintile 5 the least deprived. CI, confidence interval.

increased significantly with increasing affluence (Figure 1b). This was mirrored by a significant fall in the percentage of patients presenting with AKI who were younger than 60 years.

Cox regression proportional hazard modeling analysis was used to assess corrected patient mortality. For the whole cohort, higher hazard of death was associated with older age (hazard ratio: 1.037; 95% CI: 1.036–1.38; $P < 0.001$) and a higher WIMD ranking (i.e., less social deprivation) (hazard ratio: 1.001; 95% CI: 1.001–1.002; $P < 0.001$). Adjusted for age, however, the hazard ratio of death was lower in patients with a higher WIMD ranking (adjusted hazard ratio: 0.999; 95% CI: 0.998–0.999; $P < 0.001$).

## Incidence of AKI by WIMD Population Age

The incidence of AKI according to patient age using the population of each WIMD geographic area within that age group as the denominator is shown in Figure 2. The data are subdivided into 4 age groups: younger than 60 years (Figure 2a), 60 to 69 years (Figure 2b), 70 to 79 years (Figure 2c), and 80 years or older (Figure 2d). In all age groups, there was a significant negative relationship by linear regression, between age-adjusted incidence of AKI and the WIMD percentile, with the highest incidence in the most socially deprived areas.

## Social Deprivation Impact on AKI-Associated Mortality Is Age Dependent

The influence of patient age on the relationship between social deprivation and 90-day mortality is shown in Figure 3. Kaplan-Meier survival curves for each age group are presented as survival by WIMD quintile, with quintile 1 representing the most socially deprived and quintile 5 the most affluent geographical areas (Figure 3a-d). Mortality is also presented as percentage mortality at 90 days for each age group by WIMD percentile (Figure 3e–h).

As would be expected, overall mean survival was longest in the cohort aged <60 years (600.1 days, 95% CI: 596.5–603.6) and fell progressively in each of the age groups 60 to 69 years (531.9 days, 95% CI: 526.1–537.8), 70 to 79 years (492.0 days, 95% CI: 487.1–497.0), and 80 years and older (387.7 days, 95% CI: 383.263–392.1, $P < 0.0001$). In patients younger than 60 years, there was no significant relationship between mortality and social deprivation expressed either as Kaplan-Meier survival curves censored at 2 years or percentage mortality at 90 days (Figure 3a and e). In contrast, in each of the patient groups aged 60 to 69 (Figure 3b and f), 70 to 79 (Figure 3c and g), and 80 years and older (Figure 3d and h), there was a significant negative impact of social deprivation on survival, with the highest mortality in each of the age groups seen in the most socially deprived areas. In each of these age groups, mean survival (censored at 2 years) was lowest in the first WIMD quintile and highest in the fifth WIMD quintile (age 60–69, mean survival quintile 1, 518.3 days 95% CI: 505.1–530.6; quintile 5, 539.8 days 95% CI: 525.1–537.8, $\chi^2$ $P = 0.024$: age 70–79, mean survival quintile 1, 488.7 days 95% CI: 477.6–499.8; quintile 5, 501.1 days 95% CI: 489.3–512.9, $\chi^2$ $P = 0.04$: age older than 80 years, mean survival quintile 1, 377.9 days 95% CI: 367.4–388.5, quintile 5, 397.5 days 95% CI: 387.7–407.4, $\chi^2$ $P = 0.016$). This suggests that patients living in socially deprived areas need to survive to 60 years or older for the impact of prolonged deprivation to translate into increased AKI mortality.

As social deprivation directly influences the incidence of AKI, and patient age influences survival, analysis of the influence of the index of deprivation

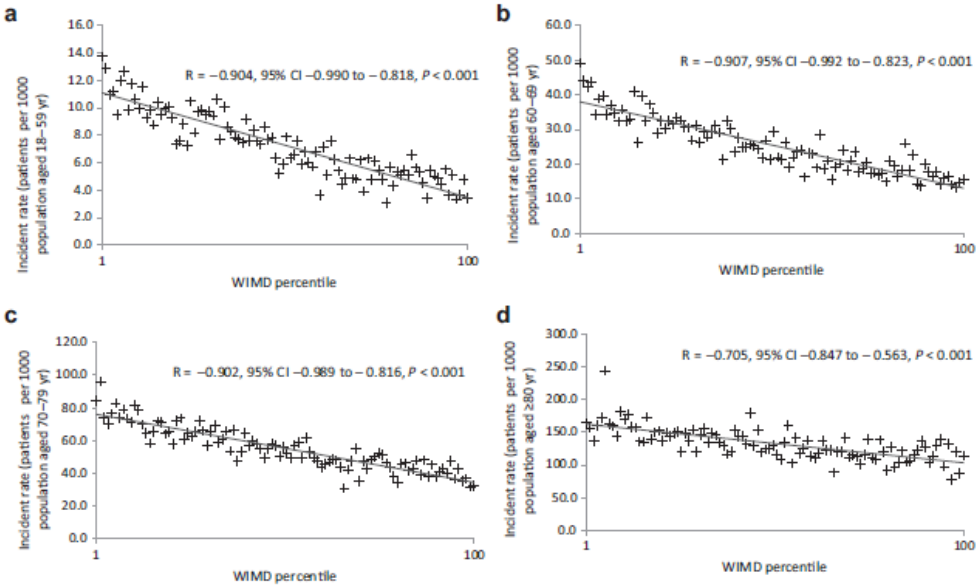


**Figure 2.** The relationship among age, incidence of acute kidney injury (AKI), and social deprivation as measured by Welsh Index of Multiple Deprivation (WIMD) percentile. The data are expressed as the incidence of AKI according to patient age using the population of each WIMD geographic area within that age group as the denominator. (a) AKI incidence rate in patients aged <60 years. (b) AKI incidence rate in patients aged 60–69 years. (c) AKI incidence rate in patients aged 70–79 years. (d) AKI incidence rate in patients aged ≥80 years. Percentile 1 is the most deprived and percentile 100 is the least deprived. CI, confidence interval.

and AKI-associated survival was also presented by a funnel plot, with patient survival reported as survival adjusted to age 60 years (Figure 4). This gives an estimate of what the survival would be if all patients in each WIMD percentile had been aged 60 at the time of the AKI episode. The plot identified 14 WIMD percentiles below the 95% confidence limits for age-adjusted survival, representing areas with excess mortality. Of these 14 percentiles, 12 represented WIMD percentiles in the lowest quarter (i.e., representing the most socially deprived). In contrast, 14 WIMD percentiles fell above 95% confidence limits for survival, representing better survival. Of these outlying WIMD percentiles with the best age-adjusted survival, 10 represented percentiles in the top quarter (i.e., the least socially deprived quarter). This is therefore consistent with social deprivation being an independent predictor of poor outcome.

### Severity of AKI

Next, we sought to examine the contribution of severity of AKI to the excess mortality in elderly patients from socially deprived areas. Severity of AKI at presentation was determined by the percentage of patients presenting with AKI stages 2 and 3. The effect of age on AKI severity is shown in Figure 5a. The percentage of patients presenting with AKI stages 2 and 3 increased in the age deciles 20 to 50 years, but thereafter, age did not alter the severity of AKI at presentation. For the whole patient group (Figure 5b), AKI severity at presentation was worse in patients from areas of social deprivation. This relationship was the same for both patients younger than 60 years (Figure 5c) and those older than 60 years (Figure 5d).

### Preexisting CKD as a Marker of Patient-Associated Comorbidities

Overall the percentage of preexisting CKD was higher in areas of affluence (Figure 6a). This is consistent with the prevalence of preexisting CKD increasing with age in patients with AKI (Figure 6b). Although there was no relationship between social deprivation and preexisting CKD in patients with AKI younger than 60 years (Figure 6c), in patients aged 60 to 69 (Figure 6d), 69 to 70 (Figure 6e), and older than 80 years (Figure 6f), social deprivation was associated with a significantly higher proportion of preexisting CKD in the patients with incident AKI.

## DISCUSSION

Socioeconomic deprivation has been shown to be an important determinant of poor health and life

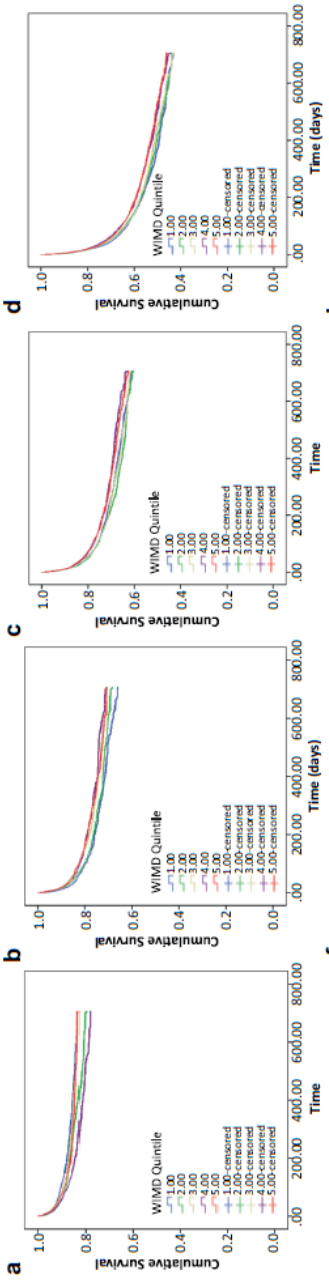


**Figure 3.** Age-dependent acute kidney injury (AKI)-associated mortality. Kaplan-Meier survival curves for AKI patients aged <60 years (a), aged 60–69 years (b), aged 70–79 years (c), and aged ≥80 years (d), stratified by Welsh Index of Multiple Deprivation (WIMD) quintile. Quintile 1 represents the most deprived and quartile 5 the most affluent ranked geographical areas. Data were censored at 2 years. Correlation between 90-day mortality and social deprivation as measured by WIMD percentile for patients with AKI aged <60 years (e), aged 60–69 years (f), aged 70–79 years (g), and aged ≥80 years (h). Percentile 1 is the most deprived and percentile 100 is the least deprived. CI, confidence interval.

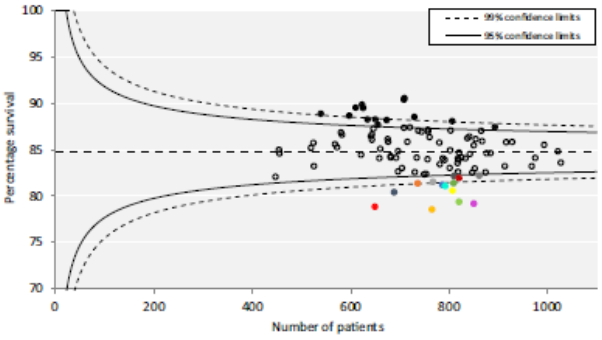


Table: 90-day survival of patients in each WIMD percentile adjusted to age 60

| WIMD Percentile | N | Adjusted 90-day survival | Limits for funnel plot: Lower 95% limit | Upper 95% limit | Lower 99% limit | Upper 99% limit |
|---|---|---|---|---|---|---|
| 100 | 539 | 88.9 | 81.7 | 87.8 | 80.7 | 88.7 |
| 88 | 597 | 88.7 | 81.9 | 87.6 | 80.9 | 88.5 |
| 83 | 610 | 89.5 | 81.9 | 87.6 | 81.0 | 88.5 |
| 96 | 623 | 89.9 | 81.9 | 87.6 | 81.0 | 88.5 |
| 84 | 625 | 89.5 | 81.9 | 87.6 | 81.0 | 88.5 |
| 87 | 634 | 88.3 | 81.9 | 87.5 | 81.1 | 88.4 |
| 3 | 649 | 78.9 | 82.0 | 87.5 | 81.1 | 88.4 |
| 60 | 650 | 88.3 | 82.0 | 87.5 | 81.1 | 88.4 |
| 94 | 655 | 87.7 | 82.0 | 87.5 | 81.1 | 88.4 |
| 90 | 673 | 88.2 | 82.0 | 87.5 | 81.2 | 88.3 |
| 8 | 688 | 80.4 | 82.1 | 87.4 | 81.2 | 88.3 |
| 72 | 708 | 90.4 | 82.1 | 87.4 | 81.3 | 88.2 |
| 89 | 709 | 90.6 | 82.1 | 87.4 | 81.3 | 88.2 |
| 64 | 729 | 88.5 | 82.1 | 87.4 | 81.3 | 88.2 |
| 18 | 736 | 81.4 | 82.1 | 87.3 | 81.3 | 88.2 |
| 26 | 765 | 78.6 | 82.2 | 87.3 | 81.4 | 88.1 |
| 5 | 767 | 81.5 | 82.2 | 87.3 | 81.4 | 88.1 |
| 19 | 786 | 81.2 | 82.2 | 87.3 | 81.4 | 88.1 |
| 24 | 792 | 81.1 | 82.2 | 87.2 | 81.4 | 88.0 |
| 69 | 806 | 88.1 | 82.3 | 87.2 | 81.5 | 88.0 |
| 14 | 807 | 80.6 | 82.3 | 87.2 | 81.5 | 88.0 |
| 56 | 809 | 81.4 | 82.3 | 87.2 | 81.5 | 88.0 |
| 10 | 810 | 82.2 | 82.3 | 87.2 | 81.5 | 88.0 |
| 7 | 820 | 79.4 | 82.3 | 87.2 | 81.5 | 88.0 |
| 4 | 820 | 81.9 | 82.3 | 87.2 | 81.5 | 88.0 |
| 1 | 850 | 79.2 | 82.3 | 87.2 | 81.6 | 87.9 |
| 9 | 861 | 82.2 | 82.3 | 87.1 | 81.6 | 87.9 |
| 75 | 898 | 87.5 | 82.4 | 87.1 | 81.6 | 87.8 |

**Figure 4.** Funnel plot for age-adjusted acute kidney injury (AKI) survival. Ninety-day survival of patients in each Welsh Index of Multiple Deprivation (WIMD) percentile is adjusted to mortality at age 60. The data in the insert provide the detail for data points that lie either below the 95% confidence limits (colored text and bullets), or above the 95% confidence limits (bold text and bullets).

expectancy.[11,23,24] In renal medicine, increased prevalence of renal failure, higher incidence of dialysis-associated mortality, reduced access to specialist care, reduced access to renal transplantation, and poorer outcomes following renal transplantation have all been reported for patients from more socioeconomically deprived

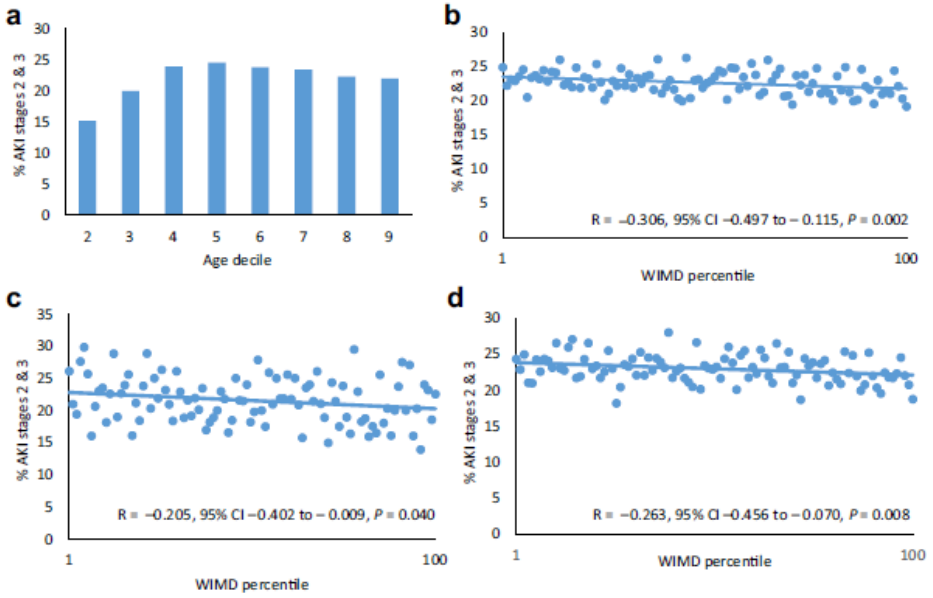


**Figure 5.** Acute kidney injury (AKI) severity. (a) Distribution of AKI stage by age. Relationship between AKI severity and social deprivation measured by Welsh Index of Multiple Deprivation (WIMD) percentile (b) for the whole cohort, (c) for patients younger than 60 years (d) and patients older than 60 years (d). Severity of AKI was assessed by the percentage presenting with AKI stages 2 and 3. Percentile 1 is the most deprived and percentile 100 is the least deprived. CI, confidence interval.

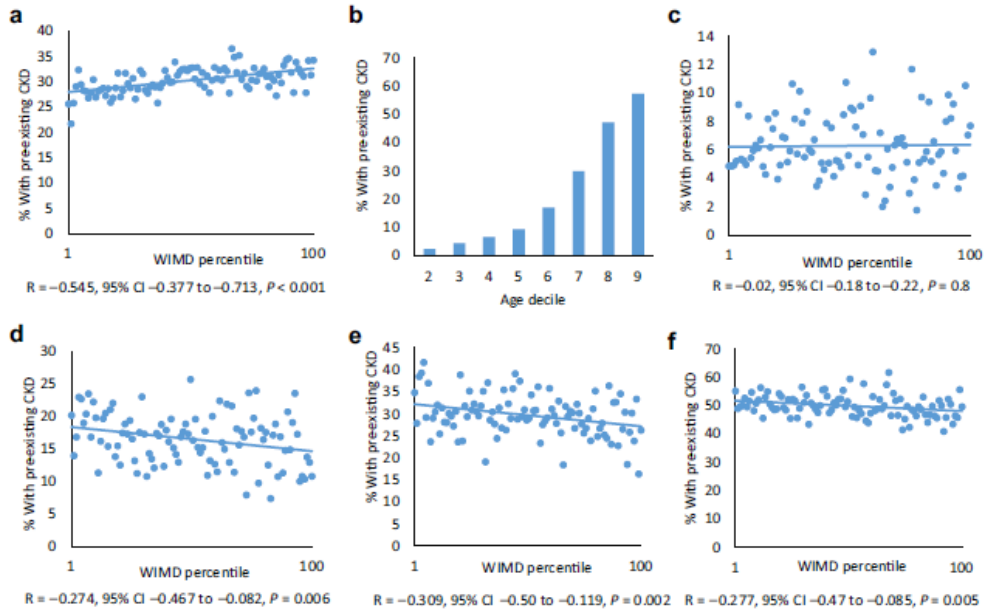


**Figure 6.** Preexisting chronic kidney disease (CKD) as a marker of patient-associated comorbidities: (a) Relationship between social deprivation and the percentage of patients with preexisting CKD for the whole cohort. (b) Distribution of preexisting CKD by age group. Relationship between social deprivation and preexisting CKD in patients with acute kidney injury younger than 60 years (c), in patients aged 60–69 (d), 69–70 (e), and older than 80 years (f). For Welsh Index of Multiple Deprivation (WIMD) percentiles, percentile 1 is the most deprived and percentile 100 is the least deprived. CI, confidence interval.

areas.[10–14,25] In this article we sought to examine the influence of age and social deprivation on outcome following AKI.

The principal findings of this study are that age is a predictor of outcome and also a predictor of the impact of social deprivation on outcome following an episode of AKI. We report a high mortality associated with AKI in affluent areas that is not due to the severity of AKI in the elderly but associated with a higher percentage of older patients who have more preexisting CKD. Previous data defining the epidemiology of AKI in Wales demonstrated increased higher hazards of death associated with older age.[7] The current data reflect this in that the AKI-associated mortality in the affluent areas is a reflection of increased life expectancy and an aging population.[26,27]

When comparing patients of a similar age, social deprivation was associated with a higher incidence of age-adjusted incidence of AKI, although in the socially deprived areas this represents smaller absolute numbers of elderly patients. It also is of note that, in patients who survive beyond age 60, social deprivation adversely affects mortality. Similarly, analysis of age-standardized mortality demonstrates that areas of social deprivation are overrepresented in the WIMD percentiles, with age-adjusted patient survival below the 95% confidence limits (i.e., the highest mortality). We postulate that the adverse influence of social deprivation in those older than 60 years is related to a greater accumulation of comorbidities. That there is more comorbidity at any particular age in deprived areas is supported by the increased proportion of CKD within each of the age groups. This is consistent with the hypothesis that socioeconomic deprivation is associated with "premature aging," which results in a difference between the "healthy life expectancy" within Wales being 18.7 years for men and 18.2 years for women in the least affluent areas. The severity of the AKI episode in the socially deprived population also contributes to the worse outcome associated with social deprivation as a higher proportion of AKI alerting at stage 2 and stage 3 at the time of presentation is associated with social deprivation. These data therefore suggest that both the burden of comorbidity and severity of AKI at presentation contribute to the impact of social deprivation on AKI-associated mortality.

Previous studies describing the impact of social deprivation on health outcomes have suggested that

patient-related health beliefs and behavior, and access to care contribute to adverse outcome. Presentation of patients from the most deprived areas, with more advanced AKI, is consistent with delayed presentation/access to medical services. Using UK-based data where health care provision is free for all at the point of delivery does, however, provide an opportunity to exclude the confounding effect of systematic access to treatment and medication. In this regard, it is perhaps reassuring that in a health care service that is free at the point of access, in our cohort for the surviving patients, deprivation appears to have no impact on renal outcomes (data not shown), although this represents a competing risk resultant from a higher death rate from the more deprived areas. It is likely that delayed access and presentation in this setting relates at least in part to patient-related behavioral factors rather than inequity of access to hospital services. Changing attitudes to encourage early presentation, however, is only one aspect of improving outcome associated with social deprivation. Encouraging and facilitating early presentation does not address the confounding effect of the increased burden of comorbidities associated with presentation of AKI and social deprivation, which also may be related to patient behaviors. For example, a higher incidence of smoking, obesity, poor diet, inactivity, and alcohol consumption associated with social deprivation,[28–33] are aetiologically linked to the 4 diseases that account for 64% of early deaths in this cohort: cancer, heart disease, stroke, and diabetes. Unhealthy patient-related behaviors are therefore likely to contribute to hypertension, obesity, and type 2 diabetes and, therefore, the increased incidence of CKD associated with AKI and social deprivation. A challenge is, therefore, to educate and support patients to make positive lifestyle changes to reduce the burden of comorbidities and improve life expectancy in socially deprived areas. In addition to access and patient behavior, biological factors, such as genetics and race, also have been found to contribute to adverse health outcomes by way of social deprivation. It is of note that Wales, however, is not ethnically diverse, with 4.1% of the population coming from minority ethnic groups, and ethnicity therefore is unlikely to influence our findings.

Although this study uses a large national data set to define the relationship between measures of social deprivation and AKI, its findings need to be qualified by its limitations. As the e-alert system is information technology driven it lacks "intelligence" and therefore there is no clinical context applied. Using an information technology–based approach precludes inclusion of clinical information, such as patient comorbidity and linkage to primary care data sets, and lacks the detail of the cause of AKI, the need for renal replacement therapy, and does not shed light on the cause of death. The study is also limited in that any patient presenting with AKI but without a measurement of renal function in the previous 365 days will not be included. Similarly, the reliance on a definition of AKI based on serial changes in serum creatinine does not take into account urine output–based AKI diagnosis, which also may lead to failure to include all cases of AKI.

In conclusion, we demonstrate that social deprivation is associated with a poor outcome following AKI. The influence of social deprivation is, however, age dependent. Social deprivation–related excess mortality was also associated with more severe disease, late presentation, and more associated comorbidity as determined by preexisting CKD. Influencing the complex and long-term inequalities that contribute to the increased incidence and mortality in AKI requires population-level social and economic interventions.

## DISCLOSURE

All the authors declared no competing interests.

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JH and DP collected and analyzed the data, produced the figures, and wrote the report. JDW, KD, 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. 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.

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**Appendix 3.8:** Published work 8 related to this thesis:

Holmes *et al*. (2017) 'Community acquired acute kidney injury: findings from a large population cohort', QJM: An International Journal of Medicine

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ORIGINAL PAPER

# Community acquired acute kidney injury: findings from a large population cohort

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## Summary

**Background:** The extent of patient contact with medical services prior to development of community acquired-acute kidney injury (CA-AKI)is unknown.
**Aim:** We examined the relationship between incident CA-AKI alerts, previous contact with hospital or primary care and clinical outcomes.
**Design:** A prospective national cohort study of all electronic AKIalerts representing adult CA-AKI.
**Methods:** Data were collected for all cases of adult (≥18 years of age) CA-AKI in Wales between 1 November 2013 and 31 January 2017.
**Results:** There were a total of 50 560 incident CA-AKI alerts. In 46.8% there was a measurement of renal function in the 30 days prior to the AKI alert. In this group, in 63.8% this was in a hospital setting, of which 37.6% were as an inpatient and 37.5% in Accident and Emergency. Progression of AKI to a higher AKI stage (13.1 vs. 9.8%, $P < 0.001$) (or for AKI 3 an increase of > 50% from the creatinine value generating the alert), the proportion of patients admitted to Intensive Care (5.5 vs. 4.9%, $P = 0.001$) and 90-day mortality (27.2 vs. 18.5%, $P < 0.001$) was significantly higher for patients with a recent test. 90-day mortality was highest for patients with a recent test taken in an inpatient setting prior to CA-AKI (30.9%).
**Conclusion:** Almost half of all patients presenting with CA-AKI are already known to medical services, the majority of which have had recent measurement of renal function in a hospital setting, suggesting that AKI for at least some of these may potentially be predictable and/or avoidable.

## Introduction

Acute kidney injury (AKI) is a common health problem worldwide, affecting up to 1% of the general population and 15% of all hospitalized patients.[1–3] Severe AKI requiring dialysis is associated with a high rate of in-hospital mortality.[4] Less severe degrees of renal injury have also been associated with a significantly heightened risk of death, prolonged in-patient hospital stay and increased costs.[5,6] AKI may also have long-lasting detrimental effects on a patient's health, with an increased incidence of subsequent Chronic Kidney Disease (CKD) and mortality.[7–10]

AKI may occur during hospitalization (HA-AKI), may be present at the time of admission to hospital or may occur and be

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managed in the community. To date the majority of published studies contributing to our understanding of epidemiology and outcome of AKI, are based on AKI in hospitalized patients.[11–13] Amongst hospitalized patients the incidence of community acquired AKI (CA-AKI) is roughly twice that of hospital acquired AKI.[14] In contrast to HA-AKI much less is known regarding the nature and impact of CA-AKI of which 30–40% is not hospitalized,[15,16] AKI within primary care and the interface between primary and secondary care. Up to half of all AKI detected by an electronic AKI alert based on a change in creatinine criteria, is accounted for by CA-AKI[15] of which only 30% is detected in primary care.[17] In this article, we have examined the relationship between incident electronic CA-AKI alerts and previous contact with either hospital services or primary care and related this to the clinical course/outcome of an AKI episode. Our aim was to highlight potential 'predictable' AKI and possible missed opportunities to minimize the risk and impact of AKI.

## Materials and methods

### Setting

Data were collected across the National Health Service in Wales which serves a population of 3.06 million. The study was approved under 'Service Evaluation Project Registration'. The previously described (and validated) Welsh electronic AKI reporting system,[15,18] utilizes the Welsh Laboratory Information Management System (LIMS) (InterSystems TrakCare Lab) to automatically compare in real time measured creatinine values on an individual patient against previous results, to generate electronic alerts using an nationally agreed algorithm based on KDIGO AKI criteria (Supplementary Figure S1).[19] Three 'rules' are applied to generate alerts differing in the time period from which the baseline creatinine is obtained. Rule 1 alerts represent a >26 μmol/l increase in SCr within the previous 48 h 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 8–365 days.

### Data collection

Data were collected for all cases of adult (≥18 years of age) CA-AKI in Wales between 1 November 2013 and the 31 January 2017. 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 30 days following the AKI alert. To prevent inclusion of known patients receiving renal replacement therapy, alerts transmitted by patients from a renal, renal transplant, or dialysis setting, and by patients who had a previous blood test in a dialysis unit were excluded.

Mortality data were collected from the Welsh Demographic Service.

### Data analysis

CA-AKI was classified as any patients with an e-alert generated in a non-in-patient setting. We defined an incident episode of AKI as 30 days, i.e. any AKI e-alert for the same patient within 30 days of a previous alert was not considered a new episode. The Medical Record Number was used as the patient identifier. This is a unique reference number allocated to each patient registered in the National LIMS and allows for multiple visits/blood test requests across all locations in Wales to be linked.

Patients were classified into two groups; those with a measurement of renal function within the preceding 30 days of the incident AKI alert (Recent test), and those without (No recent test). Alerts for the latter group were all therefore generated by a baseline creatinine value derived from the median of results from the last 30–365 days.

Progression of AKI was defined as a peak AKI stage higher than that associated with incident e-alert or for Stage 3 alerts an increase ≥50% from the Serum Creatinine (SCr) value generating the alert. Critical care admission was also used as a surrogate marker for disease severity, and was defined as a measurement of renal function in an Intensive Care Unit (ICU) setting during the 30-day AKI episode. Pre-existing CKD (PeCKD) was defined as an eGFR (calculated by CKDEpi eGFR formula)[20] < 60 ml/min/1.73 $m^2$ derived from the baseline SCr.

Statistical analysis was carried out using SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student's t test and ANOVA were used for analysis of normally distributed data. Categorical data were compared using a Pearson chi-squared test. P values < 0.05 were considered statistically significant differences.

## Results

Over the study period there were a total of 50 560 incident CA-AKI alerts. The demographic data on the cohort is shown in Table 1.

### CA-AKI and measurement of renal function in preceding 30 days

Characteristics of patients with a recent measurement of renal function (Recent test) and those without a recent measurement of renal function (No recent test) are shown in Table 1. 46.8% (23 658) of all CA-AKI had a measurement of renal function during the 30-day period prior to the AKI alert. The cohort of 'Recent test' patients at the time of the incident alert, were significantly older (70.3 ± 16.4 vs. 68.9 ± 18.5 years, P < 0.001), had a higher proportion of male patients (48.2 vs. 42.8%, P < 0.001), a higher proportion of pre-existing CKD (37.9 vs. 30.9%, P < 0.001), and a higher proportion of AKI 1 vs. AKI2/3 (recent test; AKI1 75% vs. no recent test; AKI1 73.2%, P < 0.001).

In this cohort of those with a previous measurement prior to the AKI episode, 63.8% of measurements were taken in a hospital setting (15 096 of 23 658), of which 37.6% were performed as an in-patient (n = 5677, mean time since previous test 10.7 ± 9.6 days), 37.5% in an Accident and Emergency (A&E) setting (n = 5667, mean time since previous test 7.3 ± 8.8 days) and 16.6% in an outpatient setting (n = 2512, mean time since previous test 13.5 ± 9.6 days). Only 30.8% of tests prior to the AKI episode in the 'recent test' cohort were performed in primary care (7285 of 23 658). The mean time since the previous result in primary care was 13.3 ± 9.7 days.

Pre-existing CKD prior to the AKI episode was highest in those with previous test results generated in primary care (46.9%) followed by patients with a result generated in A&E (33.6%) and patients with a test of renal function in an in-patient setting (31.5%, P < 0.001 for all comparisons). In contrast the highest proportion of AKI1 was seen in patients previously monitored in A&E (78.8%) followed by primary care (75.5%) and an in-patient setting (73.2%, P < 0.001 for all comparisons) (Table 2) .

### Clinical setting of AKI detection

The clinical location of AKI alerts is shown in Table 3. For the cohort of patients with no recent test a higher proportion of AKI

**Table 1.** Comparison of CA-AKI patients with a measurement of renal function within the preceding 30 days of an alert (Recent test) vs. those without a measurement of renal function within the preceding 30 days of an alert (No recent test)

| Variable | All CA-AKI | No recent test | Recent test | P value (recent test vs. no recent test) | 'Recent test' cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Previous test in primary care (PC) | Previous test as an inpatient (IP) | Previous test at A&E (AE) | P value ('Recent test' groups) |
| Number of episodes | 50560 | 26902 | 23658 | | 7285 | 5677 | 5667 | |
| Mean age ±SD (years) | 69.6 ±17.6 | 68.9 ±18.5 | 70.3 ±16.4 | $P < 0.001$ | 74.1 ±14.1 | 69.8 ±16.9 | 69.8 ±17.4 | $P < 0.001$ |
| Males, *n* (%) | 22933 (45.4) | 11527 (42.8) | 11406 (48.2) | $P < 0.001$ | 3337 (45.8)* | 2818 (49.6) | 2748 (48.5) | *$P = 0.002$ vs. AE&IP |
| Pre-existing CKD, *n* (%) | 17212 (34.2) | 8303 (30.9) | 8909 (37.9) | $P < 0.001$ | 3405 (46.9) | 1766 (31.2) | 1904 (33.6) | $P < 0.001$ for all |
| AKI Stage 1, *n* (%) | 37424 (74.0) | 19686 (73.2) | 17738 (75.0) | $P < 0.001$ AKI1 | 5499 (75.5)*# | 4157 (73.2)# | 4468 (78.8) | AKI1 vs. AKI2/3 |
| AKI Stage 2, *n* (%) | 8020 (15.9) | 4429 (16.5) | 3591 (15.2) | vs. AKI2/3 | 1113 (15.3) | 980 (17.3) | 807 (14.2) | *$P = 0.003$ vs. IP |
| AKI Stage 3, *n* (%) | 5116 (10.1) | 2787 (10.4) | 2329 (9.8) | | 673 (9.2) | 540 (9.5) | 392 (6.9) | #$P < 0.001$ vs. AE |
| Admission to ICU, *n* (%) | 2600 (5.1) | 1308 (4.9) | 1292 (5.5) | $P = 0.002$ | 337 (4.6) | 384 (6.8) | 341 (6.0) | n/s |
| Progression of AKI, *n* (%) | 5734 (11.3) | 2633 (9.8) | 3101 (13.1) | $P < 0.001$ | 986 (13.5)* | 756 (13.3)* | 678 (12.0) | $P = 0.02$ vs. A&E |
| 90 day mortality, *n* (%) | 11285 (22.6) | 4947 (18.5) | 6338 (27.2) | $P < 0.001$ | 1953 (26.9) | 1744 (30.9)* | 1505 (26.8) | *$P < 0.001$ |

Baseline eGFR data were missing for 198 episodes (69, No recent test; 129, Recent test; 18, PC; 8, IP; 5, A&E) and excluded from analysis of the Pre-existing CKD variable. Mortality data was available for 50022 episodes (26715, No recent test; 23307, Recent test; 7262, PC; 5643, IP; 5609, A&E). CA-AKI, Community acquired AKI; PeCKD, pre-existing chronic kidney disease; ICU, Intensive Care Unit; PC, Primary Care; IP, Inpatient; A&E, Accident and Emergency.

**Table 2.** Clinical location of blood test taken prior to and within 30 days of incident AKI episode

| Clinical location of previous test | Number of CA-AKI episodes | % of all CA-AKI episodes | Mean time from previous test to AKI episode ± SD (days) |
|---|---|---|---|
| No recent test | 26902 | 53.2 | |
| GP Practice | 7285 | 14.4 | 13.3 ±9.7 |
| Inpatient | 5677 | 11.2 | 10.7 ±9.6 |
| A&E | 5667 | 11.2 | 7.3 ±8.8 |
| Out patient | 2512 | 5.0 | 13.5 ±9.6 |
| Day case | 1240 | 2.5 | 10.4 ±8.6 |
| Other* | 1099 | 2.2 | 9.6 ±9.7 |
| Private patient | 98 | 0.2 | 8.2 ±8.1 |
| Research and Development | 42 | 0.1 | 6.9 ±8.0 |
| Ante-natal | 38 | 0.1 | 14.2 ±11.0 |
| **Total** | **26902** | **100.0** | **10.9 ±9.7** |

*Other included the following patient types: Other, Renal, Renal and Transplant, Renal Dialysis, Community, Genito-Urinary Medicine, Family Planning, Environmental, Home Office, and Occupational Health.

was detected in primary care (38.4 vs. 23.5%, $P < 0.001$) and less at A&E (48.3 vs. 55.7%, $P < 0.001$), than those with a recent test.

Within the recent test cohort, an A&E presentation with the incident AKI episode was significantly more likely for patients with previous A&E testing prior to the AKI alert (81.0%) compared with previous in-patient testing prior to the AKI alert (60.2%, $P < 0001$) which was significantly greater than for primary care tested patients (47.9%, $P < 0.001$).

In contrast presentation to primary care with the incident AKI episode was significantly greater for patients with previous primary care testing (43.2%) compared with previous in-patient testing (19.2%, $P < 0.001$), which was significantly greater than for patients previously tested at A&E (10.3%, $P < 0.001$).

## Response to and impact of AKI

The clinical location of the blood test immediately following the AKI alert is shown in Table 4. Patients who did not have a test result in the 30 days prior to the incident AKI alert were less likely to have a repeat blood test after the incident AKI alert than those known to medical services previously (81.0 vs. 88.9%, $P < 0.001$). For those who did have a repeat blood test following the incident AKI episode the time to repeat was significantly shorter for the known cohort (known 6.4 ± 12.0 vs. 10.2 ± 17.3 days $P < 0.001$), this relationship was consistent for the groups in which the repeat blood test was undertaken in Primary care (known 12.4 ± 14.2 vs. 17.6 ± 19.3 $P < 0.001$), A&E (known 6.4 ± 12.3 vs. 7.5 ± 16.5 days $P < 0.001$) or in an in-patient setting (known 2.3 ± 5.5 vs. 3.1 ± 8.3 days, $P < 0.001$).

A higher proportion of those not known, following the incident AKI episode remain in primary care for subsequent blood tests (24.2 vs. 16.5%, $P < 0.001$), and a lower proportion are admitted as an in-patient to hospital (29.9 vs. 36.1%, $P < 0.001$) than those who were known to medical services.

In the patients with a blood test prior to the AKI alert either in A&E or in an in-patient setting a higher proportion were likely to be seen in hospital (either at A&E or as an in-patient) for retesting of renal function following an AKI alert than those in whose previous measurement of renal function was undertaken in primary care (69.2 vs. 50.1% $P < 0.001$), in which a higher proportion had renal function re-measured in primary care following the alert (30.2 vs. 10.4%, $P < 0.001$).

Overall 90-day mortality for CA-AKI was 22.6%. Progression of AKI to a higher AKI stage (or for AKI 3 an increase ≥50% from the SCr generating the alert) was greater in the cohort of patients previously known to medical services (13.1 vs. 9.8%, $P < 0.001$). The proportion of patient admitted to ICU was also higher in this group (5.5 vs. 4.9%, $P = 0.001$). In addition 90-day mortality was also significantly higher for patients already 'known' to medical services compared with those with no blood test in the 30-days prior to the AKI alert (27.2 vs. 18.5%, $P < 0.001$). In the cohort of 'known' patients at the time of the incident alert (i.e. a blood test within 30 days), mortality was higher in those seen prior to the AKI episode as an in-patient (30.9%) than either those seen prior in Primary care (26.9%, $P < 0.001$ vs. in-patient) or seen previously at A&E (26.8%, $P < 0.001$ vs. in-patient).

**Table 3.** Clinical location of AKI alert

| Clinical location of AKI alert, *n* (%) | All CA-AKI | No recent test | Recent test | *P* value (recent test vs. no recent test) | 'Recent test' cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Previous test in primary care | Previous test as an inpatient | Previous test at A&E | *P* value ('Recent test' groups) |
| A&E | 26149 (51.7) | 12980 (48.3) | 13169 (55.7) | $P < 0.001$ | 3488 (26.5) | 3417 (25.9) | 4592 (34.9) | $P < 0.001$ for all |
| GP practice | 15905 (31.5) | 10334 (38.4) | 5571 (23.6) | $P < 0.001$ | 3144 (56.4) | 1092 (19.6) | 583 (10.5) | $P < 0.001$ for all |
| Out patient | 5224 (10.3) | 2729 (10.1) | 2495 (10.6) | n/s | 439 (17.6) | 617 (24.7) | 255 (10.2) | $P < 0.001$ for all |
| Day case | 1716 (3.4) | 342 (1.3) | 1374 (5.8) | $P < 0.001$ | 100 (7.3) | 290 (21.1) | 123 (9.0) | $P < 0.001$ for all |
| Other[a] | 1306 (2.6) | 437 (1.6) | 869 (3.7) | | 107 (12.3) | 228 (26.2) | 100 (11.5) | |
| Private Patient | 148 (0.3) | 47 (0.8) | 101 (0.4) | $P < 0.001$ | 3 (3.0) | 23 (22.8) | 6 (5.9) | |
| Ante-natal | 68 (0.1) | 21 (0.1) | 47 (0.2) | $P < 0.001$ | 3 (6.4) | 7 (14.9) | 1 (2.1) | |
| Research and development | 44 (0.1) | 12 (0.04) | 32 (0.1) | $P < 0.001$ | 1 (3.1) | 3 (9.4) | 7 (21.9) | |
| **Total** | **50 560** | **26 902** | **23 658** | | **7285** | **5677** | **5667** | |

[a]Other included the following patient types: Other, Renal, Renal and Transplant, Renal Dialysis, Community, Genito-Urinary Medicine, Family Planning, Environmental, Home Office, and Occupational Health.

**Table 4.** Clinical location of blood test following the incident AKI alert

| Clinical location of repeat test, *n* (%) mean time to repeat test ± SD (days) | All CA-AKI | No recent test | Recent test | *P* value (Recent test vs. No recent test) | 'Recent test' cohort | | |
|---|---|---|---|---|---|---|---|
| | | | | | Previous test in primary care | Previous test as an inpatient or at A&E | *P* value ('Recent test' groups) |
| Inpatient | 16579 (32.8) | 8032 (29.9) | 8547 (36.1) | $P < 0.001$ | 2309 (27.0) | 4905 (57.4) | $P < 0.001$ |
| | 2.7 ± 7.1 | 3.1 ± 8.3 | 2.3 ± 5.7 | $P < 0.001$ | 2.2 ± 5.5 | 2.2 ± 5.5 | n/s |
| GP practice | 10396 (20.6) | 6503 (24.2) | 3893 (16.5) | $P < 0.001$ | 2199 (56.5) | 1182 (30.4) | $P < 0.001$ |
| | 15.9 ± 18.1 | 17.6 ± 19.3 | 13.1 ± 15.5 | $P < 0.001$ | 12.4 ± 14.2 | 13.9 ± 17.4 | $P = 0.007$ |
| A&E | 9998 (19.8) | 4955 (18.4) | 5043 (21.3) | $P < 0.001$ | 1408 (27.9) | 2947 (58.4) | $P < 0.001$ |
| | 6.4 ± 4.3 | 7.5 ± 16.5 | 5.4 ± 11.8 | $P < 0.001$ | 4.3 ± 11.5 | 6.0 ± 12.1 | $P < 0.001$ |
| No repeat test | 7923 (15.7) | 5306 (19.7) | 2617 (11.1) | $P < 0.001$ | 853 (32.6) | 1348 (51.5) | n/s |
| Out patient | 2788 (5.5) | 1245 (4.6) | 1543 (6.5) | $P < 0.001$ | 266 (17.2) | 470 (30.5) | n/s |
| | 19.7 ± 21.2 | 26.8 ± 23.7 | 14.0 ± 16.9 | $P < 0.001$ | 21.3 ± 21.9 | 13.1 ± 17.6 | $P < 0.001$ |
| Other[a] | 1431 (2.8) | 522 (1.9) | 909 (3.8) | $P < 0.001$ | 169 (18.6) | 211 (23.2) | |
| | 9.8 ± 15.9 | 12.8 ± 19.4 | 8.1 ± 13.2 | $P < 0.001$ | 7.6 ± 13.7 | 6.2 ± 12.3 | n/s |
| Day case | 1291 (2.6) | 288 (1.1) | 1003 (4.2) | $P < 0.001$ | 76 (7.6) | 260 (25.9) | $P < 0.001$ |
| | 9.6 ± 12.4 | 15.2 ± 17.3 | 8.1 ± 10.1 | $P < 0.001$ | 7.6 ± 11.0 | 7.6 ± 13.0 | n/s |
| Private patient | 87 (0.2) | 33 (0.1) | 54 (0.2) | $P < 0.001$ | 2 (3.7) | 7 (13.0) | n/s |
| | 7.9 ± 15.7 | 12.8 ± 19.9 | 5.1 ± 12.1 | $P = 0.034$ | 10.4 ± 14.7 | 5.7 ± 8.0 | n/s |
| Research and development | 37 (0.1) | 7 (0.03) | 30 (0.1) | $P < 0.001$ | | 6 (20.0) | |
| | 3.4 ± 8.6 | 8.6 ± 18.2 | 2.3 ± 4.1 | n/s | | 2.0 ± 2.8 | |
| Ante-natal | 30 (0.1) | 11 (0.04) | 19 (0.1) | $P < 0.001$ | 3 (15.8) | 8 (42.1) | n/s |
| | 8.9 ± 16.2 | 17.3 ± 25.0 | 4.1 ± 3.2 | $P = 0.030$ | 3.5 ± 2.0 | 4.5 ± 3.8 | n/s |
| **Total** | **50 560** | **26 902** | **23 658** | | 7285 | 11 344 | |
| | **8.3 ± 15.0** | **10.2 ±17.3** | **6.4 ± 12.0** | **$P < 0.001$** | 7.1 ± 12.7 | 5.4 ± 11.5 | **$P < 0.001$** |

[a]Other included the following patient types: Other, Renal, Renal and Transplant, Renal Dialysis, Community, Genito-Urinary Medicine, Family Planning, Environmental, Home Office, and Occupational Health.

## Discussion

Despite advances in health care, the incidence of AKI is increasing both in the UK[21,22] and USA.[23,24] Potential explanations for this increase may be related to increasingly aggressive medical and surgical therapies in a largely aging population with multiple comorbid conditions.[25] The significance of AKI is highlighted by the increase in mortality associated with even small changes in SCr.[26–28] In contrast to HA-AKI less is known regarding CA-AKI although it is clear that CA-AKI is a major contributor to the overall disease burden.[13,29] In this manuscript we provide a novel insight into the nature and outcome of CA-AKI and the patient journey in the days and weeks prior to and immediately following the detection of AKI.

The first notable finding in this study is that almost half of the patients who generated a CA-AKI alert have a measurement of renal function in the 30 days preceding the alert. For the majority of these patients this measurement was undertaken within two weeks of the incident AKI episode. As might be

expected this group was older and had a higher proportion of CKD suggesting that this is a group with higher co-morbidity and therefore AKI risk factors. In keeping with this, mortality was also higher in patients which were known to medical services prior to development of AKI, at least as judged by a recent test of renal function. Of those with a recent test, for more than half, the review and measurement of renal function had been undertaken in a hospital setting. Although labelled as CA-AKI, given the short time frame between test and AKI incident alert it is possible that the incident AKI episode was related to either the illness precipitating the consultation or change made in response to the presenting symptoms. It is interesting therefore to speculate that within this group that AKI is some cases at least was predictable and therefore potentially avoidable. Within the group with a 'recent test' the highest mortality was seen in patients who had a measurement of renal function in an inpatient setting within roughly a fortnight of the AKI episode. This was also the group with the highest incidence of de-novo AKI (i.e. the lowest proportion of pre-existing CKD). The lower mortality in patients monitored in primary care prior to the AKI episode reflects the highest proportion of acute on chronic AKI, whilst the lower mortality in those with a measurement of renal function at A&E prior to the AKI episode reflect less severe AKI at presentation which may also reflect the shortest time interval between the previous measured renal function and the AKI episode suggesting early presentation.

Although this study highlights a large cohort of patients who develop AKI following recent hospital attendance, a weakness is its dependence of an e-alert system which lacks clinical context. Further work is therefore required to understand the relationship between medical service interactions/interventions, patient inter-current illness and their contribution to the development of CA-AKI, to identify any intervention or patient-related risk factors which in particular might highlight who among the recent hospital attendees might be at risk and potentially benefit from early clinical review. Recent data however, derived from a cohort of patients with HA-AKI have identified five clusters of diagnoses to be associated with development of AKI: sepsis, heart disease, poly-trauma, liver disease and cardiovascular surgery.[30] This suggests that patients recently discharged back to the community following hospital attendance for these indications may benefit from early clinical review to facilitate early detection, prompt re-assessment of patients, close monitoring of patient physiology, review of medication or consideration of hospitalization in an attempt to improve patient outcomes.

Although presentation to A&E is the most common presentation for CA-AKI, for those without a recent test the likelihood of presentation to primary care with the incident episode of AKI was higher. For patients in whom renal function was recently measured the site of presentation with the incident AKI episode also reflected where the previous blood test was undertaken, such that a previous recent blood test in A&E predicted presentation to A&E with the incident AKI episode and similarly a recent blood test in primary care predicted those who presented to primary care with the AKI episode. This suggests that patients when acutely unwell are most likely to return to a 'familiar' port of call for health advice. Our data also suggest that patients who have had recent measurement of renal function are more likely to have a repeat measurement following an AKI alert and that the time to a repeat blood test for this group is also significantly shorter. It is likely that this reflects both patient as well as medical staff-related behavioural factors. The place of detection of AKI also influences the likelihood of hospital admission with AKI detected in primary care generating the lowest number of admissions. This is consistent with our previous data on AKI in primary care which demonstrated that admission from primary care was associated with AKI severity.[17] Although admission was associated with higher mortality it was of note that in surviving patients non-admission was associated with worse renal outcomes, and that patients who were not hospitalized had a lower rate of renal recovery and a greater likelihood of developing an eGFR <60 ml/min/1.73 $m^2$ for the first time, which may be indicative of development of *de novo* CKD.[15] This is also consistent with the recent report of Sawheny in which non-admitted AKI whilst having a lower mortality was associated with greater non-recovery of renal function.[31] Previous data suggest that 'non-admission' is at least in part is due to lack of recognition of the significance of the alert.[14–16] Furthermore, we have demonstrated that a delayed response to the alert in primary care is associated with a significantly worse renal outcome.[17] Based on these observations we have previously recommended that a clinical review or referral together with a repeat measurement of renal function within 7 days should be considered an appropriate response to AKI e-alerts in primary care.

In conclusion this study demonstrates that almost half of all patients presenting with CA-AKI are already known to medical services, suggesting that AKI for at least some of these may be potentially predictable and/or avoidable. Of these almost two thirds have a recent interaction with hospital either as an inpatient or via an A&E visit, thus suggesting that a sizable proportion of what is currently labelled as CA-AKI may in fact relate to recent 'hospitalization' and may not actually be 'CA'. The challenge is to identify the group of patients in whom AKI may be predictable and for whom early clinical review is likely to reduce the incidence of or alter the outcome following AKI.

## Supplementary material

Supplementary material is available at *QJMED* online.

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**Appendix 3.9:** Published work 9 related to this thesis:

Phillips *et al*. (2017) 'Seasonal pattern of incidence and outcome of Acute Kidney Injury: A national study of Welsh AKI electronic alerts', The International Journal of Clinical Practice

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ORIGINAL PAPER

WILEY THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

# Seasonal pattern of incidence and outcome of Acute Kidney Injury: A national study of Welsh AKI electronic alerts

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## Summary

**Objectives:** To identify any seasonal variation in the occurrence of, and outcome following Acute Kidney Injury.

**Methods:** The study utilised the biochemistry based AKI electronic (e)-alert system established across the Welsh National Health Service to collect data on all AKI episodes to identify changes in incidence and outcome over one calendar year (1st October 2015 and the 30th September 2016).

**Results:** There were total of 48 457 incident AKI alerts. The highest proportion of AKI episodes was seen in the quarter of January to March (26.2%), and the lowest in the quarter of October to December (23.3%, $P < .001$). The same trend was seen for both community-acquired and hospital-acquired AKI sub-sets. Overall 90 day mortality for all AKI was 27.3%. In contrast with the seasonal trend in AKI occurrence, 90 day mortality after the incident AKI alert was significantly higher in the quarters of January to March and October to December compared with the quarters of April to June and July to September ($P < .001$) consistent with excess winter mortality reported for likely underlying diseases which precipitate AKI.

**Conclusions:** In summary we report for the first time in a large national cohort, a seasonal variation in the incidence and outcomes of AKI. The results demonstrate distinct trends in the incidence and outcome of AKI.

## 1 | INTRODUCTION

AKI is a clinical syndrome characterised by rapid loss of kidney function, and is associated with adverse patient outcomes.[1-5] It is estimated to occur in up to 15% of hospitalised patients and up to 60% of critically ill patients.[2,3,6] The estimated cost of AKI to NHS England is £1 billion/year or roughly 1% of the total NHS budget.[7]

Significant weaknesses in patient management have been widely reported.[8,9] In the UK, the National Confidential Enquiry report highlighted sub-optimal care of AKI patients which may subsequently translate into episodes of preventable harm.[10] This has driven initiatives to facilitate early detection and intervention in order to improve patient outcomes. In response the Royal College of Physicians, at a consensus conference in the UK, recommended the adoption of an e-alert system to aid in the early identification of AKI.[11] The presumed benefits of early detection of AKI have led to the development of an automated an AKI electronic alert system in Wales, and the other home countries of the United Kingdom.[12] Electronic alerts are generated by comparing a single serum creatinine measurement with previous measurements for the same patient, and flagging any results which represent a rise in creatinine equating AKI.[13] In addition to prompting clinicians to intervene at an early stage, this also provides a valuable source of data regarding the epidemiology of AKI. We have previously used this dataset to report the incidence and outcome of AKI in adult[14] and paediatric

Dafydd Phillips and Oliver Young made an equal contribution to this manuscript

  

patients[15] in Wales (UK). More recently we have demonstrated the significance of the electronic AKI alert in primary care.[16]

Despite advances in healthcare, the incidence of AKI is increasing both in the UK[17,18] and USA.[19,20] Potential explanations for this increase may be related to increasingly aggressive medical and surgical therapies in a largely aging population with multiple comorbid conditions.[21] In the majority of cases AKI is a secondary to other disease states and critical illness rather than a reflection of primary intrinsic renal disease. Alterations in the patterns of these underlying diseases may therefore also contribute to the increased incidence of AKI. Seasonal variations have been described in many diseases which may precipitate AKI. In contrast with date there are no studies which address seasonal variations in the incidence and outcome of AKI. Using our dataset generated from electronic AKI alerts in this manuscript we describe the seasonal trends for AKI over a one year period. The data captures all cases of AKI in both community and hospital settings with AKI being defined by change in creatinine criteria.

**What's known**

- Seasonal variation in diseases associated with the development of AKI has been previously reported.

**What's new**

- This is the first study to describe seasonal variation in the number of AKI cases and associated mortality.

## 2 | METHODS

### 2.1 | Electronic reporting of AKI

The previously described (and validated) Welsh electronic AKI reporting system,[22] utlitises the Welsh laboratory information management system (LIMS), (InterSystems TrakCare Lab, Cambridge, MA) to automatically compare in real time measured creatinine values on an individual patient against previous results. This generates electronic AKI alerts, derived from a nationally agreed algorithm based on KDIGO AKI criteria.[12]

The study was approved under Service Evaluation Project Registration.

### 2.2 | Data collection

Data were collected for all cases of adult (≥18 years of age) AKI in Wales between 1st October 2015 and the 30th September 2016, and organised into quarters. The "calendar" year was divided into four quarters: January to March (Jan-Mar), April to June (Apr-Jun), July to September (Jul-Sep) and October to December (Oct-Dec). 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 30 days following the AKI alert. To prevent inclusion of known patients receiving renal replacement therapy, alerts transmitted by patients from a renal, renal transplant, or dialysis setting, and by patients who had a previous blood test in a dialysis unit were excluded.

Mortality data were collected from the welsh demographic service (WDS). Patients were censored at 1 year for survival analysis.

### 2.3 | Data analysis

All patients for which the first alert was issued during a hospital admission who also had a normal SCr value generated in a hospital setting within the preceding 7 days were defined as hospital acquired (HA)-AKI. Patients alerting in a non-inpatient setting (including Accident and Emergency/Acute assessment units) and not alerting in primary care were classified as non-primary care community acquired (CA)-AKI. Primary care and non-primary care CA-AKI therefore collectively represent CA-AKI. Hospitalisation of CA-AKI, was defined as a measurement of renal function in a hospital setting within 7 days following the AKI e-alert. 4399 (9.1%) patients whilst alerting in an inpatient setting had no results for the previous 7 days. As these patients did not therefore fall into either CA- or HA- definitions, they were excluded from the subgroup analysis.

An incident AKI episode was defined as 30 days ie any AKI e-alert for the same patient within 30 days the incident alert was not considered a new episode. Progression of AKI was defined as a peak AKI stage higher than that associated with incident e-alert or for stage 3 alerts an increase ≥50% from the SCr generating the alert. Pre-existing chronic kidney disease (PeCKD) was defined as an eGFR (calculated by CKDEpi eGFR formula[23]) <60 mL/min/1.73 $m^2$ derived from the baseline SCr.

Statistical significance was determined by one way ANOVA, student $t$ test and $\chi^2$ test as appropriate. The influence of age, sex and pre-existing CKD on AKI incidence was assessed by logistic regression. $P$-values less than 0.05 were considered statistically significant.

## 3 | RESULTS

### 3.1 | Seasonal trends in AKI episodes

Over the study period there were a total of 48 457 incident AKI alerts, and a progressive fall in the number of AKI episodes in each quarter of the calendar year (Table 1 and Figure 1A), with the proportion of AKI falling from 26.2% in the quarter of Jan-Mar to 23.3% in the quarter of Oct-Dec ($P < .001$). The seasonal trend in AKI occurrence was not associated with differences in basic patient demographic as assessed by sex, age or pre-existing CKD (Table 1). In a logistic regression model age, gender and pre-existing CKD had no influence on the primary outcome ie seasonal variation in AKI. As a results age adjusted incidence of AKI in each season also demonstrated a fall from 25.9% in Jan-Mar to 23.8% in Oct-Dec ($P < .001$).

#### 3.1.1 | Incidence of CA-AKI

Of all AKI which occurred during the study period 49.9% were CA-AKI alerts (Table 2). This represents a total of 24 178 alerts. The number

**TABLE 1** Seasonal changes in number, patient characteristics, AKI stage and outcome of all AKI episodes

| | Annual total | Jan-Mar | Apr-Jun | Jul-Sep | Oct-Dec | *P*-value |
|---|---|---|---|---|---|---|
| No. of episodes, n (% of total) | 48 457 | 12 674 (26.2) | 12 329 (25.4) | 12 116 (25.0) | 11 338 (23.4) | $P < .001$ |
| Mean age (y) | 70.4 | 70.8 | 70.1 | 70.2 | 70.2 | n/s |
| Proportion of males, n (%) | 22 861 (47.2) | 5990 (47.3) | 5853 (47.5) | 5669 (46.8) | 5349 (47.2) | n/s |
| % with pre-existing CKD | 33.1 | 34.2 | 32.3 | 32.9 | 32.9 | n/s |
| AKI stage, n (%) | | | | | | |
| AKI1 | 37 405 (77.2) | 9655 (76.2) | 9476 (76.9) | 9510 (78.5) | 8767 (77.3) | n/s |
| AKI2 | 7157 (14.8) | 1924 (15.2) | 1873 (15.2) | 1679 (13.9) | 1681 (14.8) | |
| AKI3 | 3895 (8.0) | 1098 (8.7) | 980 (7.9) | 927 (7.7) | 890 (7.8) | |
| 90 d mortality, n (%) | 13 080 (27.3) | 3694 (29.4) | 3179 (26.1) | 3061 (25.6) | 3146 (28.1) | $P < .001$ Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep |

of CA-AKI episodes varied across the year (Figure 1B). The highest number (6265) was seen in Jan-Mar, and there were significantly fewer episodes (5632) during the Oct-Dec compared with each of the preceding quarters ($P < .001$ for comparison of Oct-Dec vs. each of the other quarters).

31.5% of CA-AKI represented alerts generated in Primary care (GP-AKI), and 48.4% represented patients alerting at the hospital front door (A&E AKI). Both cohorts demonstrated the same seasonal trends with a significantly lower number of AKI alerts in Oct-Dec (Table 2). Only 42.9% of all CA-AKI were admitted to hospital following the alert. The same seasonal trends seen in the whole cohort (with the lowest number seen in Oct-Dec) was also seen in both the admitted and non-admitted groups (Table 2).

#### 3.1.2 | Incidence of HA-AKI

Of all AKI that occurred during the study period 41.0% were HA-AKI alerts (Table 3). This represents a total of 19 880 alerts. The number of hospital acquired AKI episodes varied across the year (Figure 1B). The number of HA-AKI episodes in Jan-Mar (5334), was statistically greater than the number of episodes in all other quarters. The comparative fall in each quarter was statistically significant, with the lowest number of cases being seen in the quarter of Oct-Dec (4569). The seasonal trend in AKI occurrence was not associated with differences in basic patient demographic as assessed by sex, age or pre-existing CKD.

In the absence of clinical data, to provide insight into the nature of HA-AKI we analysed the seasonal incidence of AKI in relation to the clinical speciality in which the alert was generated (Table 4). Only specialities in which ≥200 AKI episodes were documented during the year were included in this analysis. The decreasing trend of AKI incidence throughout the calendar year was significant in the majority of the medical specialties, the exceptions being haematology/oncology and endocrinology. It should, however, be noted that these two specialties also had the fewest number of episodes. Within the surgical specialties the pattern of falling numbers was seen in General surgical and urology locations only, and no seasonal changes in AKI occurrence was seen related to trauma, obstetrics and gynaecology nor cardiothoracic location codes.

### 3.2 | Seasonal trends in AKI outcomes

Overall 90 day mortality for all AKI was 27.3% (Table 1). 90 day mortality after the incident AKI alert was significantly higher in the quarters of Jan-Mar and Oct-Dec compared with the Apr-Jun and Jul-Sep quarters ($P < .001$).

#### 3.2.1 | CA-AKI

90 day mortality was also significantly higher following an incident CA-AKI alert, in the Jan-Mar and Oct-Dec quarters (Table 2). CA-AKI severity was also highest in these quarters with a higher proportion of AKI stage 2/3. ICU admission was also used as a surrogate marker of disease severity. In the same two quarters a higher proportion of AKI episodes required support in an intensive care unit (ICU) setting.

#### 3.2.2 | HA-AKI

As with CA-AKI, 90 day mortality was significantly higher following an alert in the Jan-Mar and Oct-Dec quarters (Table 3). For this subgroup, however, there was no significant difference in AKI severity throughout the year, as assessed by AKI stage at presentation, and the proportion of patients requiring support in the ICU.

## 4 | DISCUSSION

The majority of publications of large series characterising AKI rely on making and recording an accurate diagnosis of AKI through hospital coding or retrospective review of hospital records.[24-27] As a result most studies of AKI focus on hospitalised patients,[4,8,24,26-29] and do not include all community acquired AKI, as a significant proportion of AKI in these settings do not result in hospitalisation.[30-34] We have previously demonstrated that using the electronic AKI

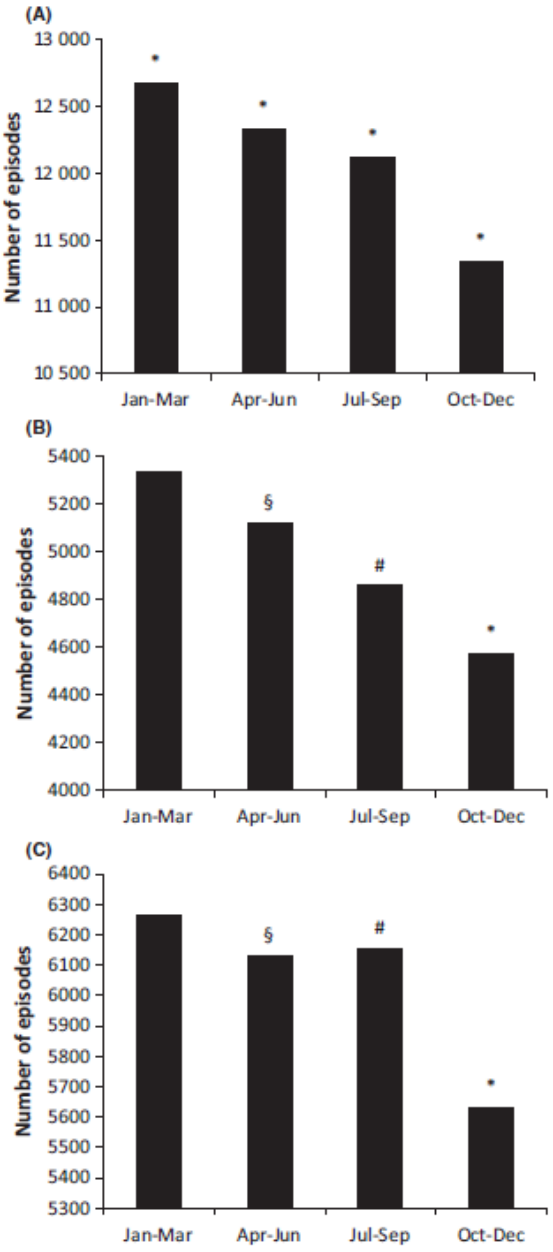


**FIGURE 1** Total incidence of AKI per quarter. (A) Total number of all cause AKI episodes per quarter. *, $P < .001$ vs. all other quarters. (B) Total number of hospital acquired AKI episodes per quarter. *, $P < .001$ vs. all other quarters; #, $P < .001$ vs. Jan-Mar; §, $P < .05$ vs. Jan-Mar. (C) Total number of community acquired AKI episodes per quarter. *, $P < .001$ vs. all other quarters; #, $P < .001$ vs. Oct-Dec and Jan-Mar; §, $P < .05$ vs. Jul-Sep and $P = .008$ vs. Jan-Mar

dataset provides a comprehensive characterisation of AKI across both community and hospital settings.[14] Our data therefore provides a comprehensive overview of trends of all cases of AKI defined by changes in serum creatinine. It should be noted, however, that any patients for which there are no results on the system existing from the previous 365 days will not be identified, although these cases may represent AKI. Currently any abnormal serum creatinine result with no baseline creatinine comparator is highlighted as an abnormal result requiring clinician scrutiny, but is not included in our data.

The data presented represent the first study to describe the seasonal variation in the number of episodes of AKI in a large national cohort. Whilst seasonal changes in disease patterns have been described for a number of illnesses, there is no published data regarding whether this affects the seasonal incidence of AKI. Our data demonstrates that there is a significant seasonal variation in the incidence of all AKI with a significant decreasing trend in the incidence throughout the calendar year.

In this manuscript it is evident that the seasonal patterns for AKI are similar for both CA-AKI and HA-AKI. For CA-AKI the trend is consistent for both the cases admitted and managed in the community, as well as those cases detected in primary care and at the hospital front door. This pattern therefore does not reflect the widely reported winter rise in emergency medical pressures in NHS hospitals across the United Kingdom which is accepted to reflect admissions related to respiratory and cardiovascular illness.[35] Within the HA-AKI AKI cohort, and in the absence of clinical data, we used the location of the AKI alerts to provide some insight into the potential causes of AKI. The seasonal trend for a fall in incidence was consistent across the majority of medical specialties. Within surgical specialties, however, the fall in the number of episodes throughout the year was seen for alerts generated in general surgical and urology location codes only and not in trauma nor cardiothoracic locations. It is interesting to speculate that in the latter two specialties clinical activity is not a reflection of "illness." Trauma cases relate to "human behaviour patterns" rather than disease and tend to reflect patterns of weather and temperature whilst cardiothoracic surgery activity generally reflects elective planned surgery which leads to a consistent number of procedures throughout the year. In contrast, for medical specialties and general surgery, clinical activity is more closely associated to "illness" rather than elective activity, although we are unable to distinguish between elective and emergency cases and this therefore remains speculative.

Whilst demonstrating a significant trend our data does not, however, provide a clear explanation for this trend as the e-alert system is IT driven and based on creatinine values only. There is therefore no clinical context which precludes inclusion of clinical information, such as patient comorbidity and linkage to primary care datasets. It also lacks the detail of the cause of AKI. In the majority of cases AKI does not represent intrinsic kidney disease but rather a response to other primary illness which leads to reduced renal perfusion. The seasonal variation in AKI incidence is therefore likely to reflect that common causes/precipitants of AKI demonstrate seasonal variation. Seasonal variation in disease presentations and hospital admissions is a well-described phenomenon. For example, acute myocardial infarction is more common during winter and spring.[36,37] Whilst the explanation for this remains unclear it is postulated that the likely link is the association between

**TABLE 2** Seasonal changes in number, patient characteristics, AKI stage and outcome of CA-AKI episodes

| | Annual total | Jan-Mar | Apr-Jun | Jul-Sep | Oct-Dec | *P*-value |
|---|---|---|---|---|---|---|
| No. of episodes, n (% of total) | 24 178 | 6265 (25.9) | 6129 (25.4) | 6152 (25.5) | 5632 (23.3) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |
| Mean age (y) | 69.4 | 70.1 | 69.2 | 69.0 | 69.1 | n/s |
| Proportion of males, n (%) | 10 995 (45.5) | 2860 (45.7) | 2799 (45.7) | 2787 (45.3) | 2549 (45.3) | n/s |
| % with pre-existing CKD | 33.2 | 34.0 | 32.3 | 33.1 | 33.7 | n/s |
| AKI stage, n (%) | | | | | | |
| AKI1 | 17 931 | 4559 (72.8) | 4584 (74.8) | 4663 (75.8) | 4125 (73.2) | *P* = .002 AKI1 vs. AKI2/3 Jan-Mar/ Oct-Dec vs. Apr-Jun/Jul-Sep |
| AKI2 | 3898 | 1048 (16.7) | 975 (15.9) | 923 (15.0) | 952 (16.9) | |
| AKI3 | 2349 | 658 (10.5) | 570 (9.3) | 566 (9.2) | 555 (9.9) | |
| AKI associated with ICU admission, n (%) | 1191 (4.9) | 320 (5.1) | 294 (4.8) | 269 (4.4) | 308 (5.5) | *P* = .04 Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep |
| 90 d mortality, n (%) | 5206 (21.8) | 1482 (23.9) | 1218 (20.1) | 1198 (19.7) | 1308 (23.6) | *P* < .001 Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep |
| CA-AKI subgroup seasonal incidence | | | | | | |
| GP-AKI, n (%) | 7626 | 1915 (25.1) | 2024 (26.5) | 2022 (26.5) | 1665 (21.8) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |
| A&E AKI, n (%) | 11 693 | 3197 (27.3) | 2867 (24.5) | 2873 (24.6) | 2756 (23.6) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |
| AKI admitted, n (%) | 10 368 | 2784 (26.9) | 2568 (24.8) | 2535 (24.5) | 2481 (23.9) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |
| CA-AKI not admitted, n (%) | 13 810 | 3481 (28.9) | 3561 (25.8) | 3617 (26.2) | 3151 (22.8) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |

**TABLE 3** Seasonal changes in number, patient characteristics, AKI stage and outcome of HA-AKI episodes

| | Annual total | Jan-Mar | Apr-Jun | Jul-Sep | Oct-Dec | *P*-value |
|---|---|---|---|---|---|---|
| No. of episodes, n (% of total) | 19 878 | 5333 (26.8) | 5120 (25.8) | 4857 (24.4) | 4568 (22.9) | *P* < .001 Oct-Dec vs. Jan-Mar/ Apr-Jun/Jul-Sep |
| Mean age (y) | 69.4 | 70.1 | 69.2 | 69.0 | 69.1 | n/s |
| Proportion of males, n (%) | 9554 (48.1) | 2567 (48.1) | 2467 (48.2) | 2291 (47.2) | 2229 (48.8) | n/s |
| % with pre-existing CKD | 33.8 | 35.2 | 33.4 | 33.8 | 32.6 | n/s |
| AKI stage, n (%) | | | | | | |
| AKI1 | 16 279 (81.9) | 4355 (81.6) | 4128 (80.6) | 4010 (82.6) | 3786 (82.9) | n/s |
| AKI2 | 2495 (12.6) | 666 (12.5) | 698 (13.6) | 593 (12.2) | 538 (11.8) | |
| AKI3 | 1106 (5.6) | 313 (5.9) | 294 (5.7) | 254 (5.2) | 245 (5.4) | |
| AKI associated with ICU admission, n (%) | 1028 (5.4) | 284 (5.6) | 245 (5.0) | 237 (5.0) | 262 (5.9) | n/s |
| 90 d mortality, n (%) | 6924 (33.2) | 1855 (35.1) | 1636 (32.3) | 1530 (31.9) | 1503 (33.2) | *P* = .003 Jan-Mar/Oct-Dec vs. Apr-Jun/Jul-Sep |

variation in temperature and biological factors which contribute to disease pathogenesis such as blood pressure[38] and other metabolic factors.[39,40] Epidemiological studies in diabetes have demonstrated that hypoglycaemic episodes are more common during summer months, whilst hyperglycaemic complications are more common in the first months of the year, with said patterns ascribed to changes in calorie consumption and physical activity.[41-43] Increased incidence of Gram-negative bacteraemia has been reported in summer months and associated with elevated monthly outdoor temperatures.[44-46] Community acquired pneumonia in contrast is more common in the spring and

**TABLE 4** Seasonal variation in HA-AKI by location (Medical specialty) of AKI alert: n (% in quarter)

| | Annual total | Jan-Mar | Apr-Jun | Jul-Sep | Oct-Dec | P-value |
|---|---|---|---|---|---|---|
| Medical specialties | | | | | | |
| Internal medicine | 5000 | 1342 (26.8) | 1258 (25.2) | 1265 (25.3) | 1135 (22.7) | $P < .001$ |
| Care of the elderly | 1946 | 533 (27.4) | 492 (25.3) | 483 (24.8) | 438 (22.5) | $P = .005$ |
| Cardiology | 1730 | 470 (27.2) | 444 (25.7) | 413 (23.9) | 403 (23.3) | $P = .03$ |
| Gastroenterology | 915 | 229 (25.0) | 251 (27.4) | 239 (26.1) | 196 (21.4) | $P = .02$ |
| Thoracic medicine | 876 | 252 (28.8) | 245 (27.9) | 214 (24.4) | 165 (18.8) | $P < .001$ |
| Haem/Oncology | 529 | 136 (25.7) | 133 (25.1) | 119 (22.5) | 141 (26.5) | n/s |
| Endocrinology | 318 | 90 (28.3) | 85 (26.7) | 79 (24.8) | 64 (20.1) | n/s |
| Surgical specialties | | | | | | |
| General surgery | 2511 | 682 (27.2) | 630 (25.1) | 596 (23.3) | 603 (24.1) | $P = .02$ |
| Trauma & Orthopaedic | 1694 | 427 (25.2) | 414 (28.7) | 422 (24.9) | 431 (25.4) | n/s |
| Urology | 703 | 177 (25.2) | 202 (28.7) | 171 (24.2) | 153 (21.7) | $P = .02$ |
| Gynaecology | 244 | 65 (26.6) | 62 (25.4) | 58 (23.8) | 59 (24.2) | n/s |
| Obstetrics | 246 | 58 (23.6) | 79 (32.1) | 53 (21.5) | 56 (22.8) | n/s |
| Cardiothoracic surgery | 237 | 64 (27.0) | 63 (26.6) | 54 (22.8) | 56 (23.6) | n/s |
| Anaesthetics/ICU | 218 | 59 (27.1) | 67 (30.7) | 51 (23.4) | 41 (18.8) | $P = .02$ |

winter, as a result of the combination of circulating respiratory bacteria being more prevalent during colder seasons, and people spending more time indoors during colder months.[47,48] Trauma is another potential predisposing factor for the development of AKI. Studies have shown that in paediatric cohorts, admissions relating to trauma are highest during summer months, presumably as children spend more time playing outdoors during these warmer months. In contrast, adults are more likely to be admitted with significant trauma during winter months, because of an increase in falls and accidents relating to ice/snow.[49] It is likely that each of these aforementioned diseases influence the seasonal variation in AKI and further studies are required focusing on the precipitating factors which lead to AKI to provide a robust link between disease aetiology and the seasonal variation that we have described. A striking and somewhat unexpected observation in this study, however, is the consistency of the seasonal trend across all of the subgroups of AKI that we have examined.

In addition to the seasonal effect of disease incidence we have also found and temporal association with outcome following AKI. There was however a disconnect between seasonal trends in incidence and outcome as mortality was highest in the first and fourth quarters of the calendar year, that is during the winter months. This is again consistent across CA- and HA-AKI. For CA-AKI mortality was associated with disease severity at presentation as the AKI stage at presentation was also higher in these two quarters, as was the need for ICU support. This association with AKI severity as assessed by these simple parameters were not however apparent for HA-AKI patients. This pattern of mortality is reflective of the accepted patterns of mortality associated with "winter pressures". Excess winter mortality has been described in studies dating back over a century,[50] with an increase in all cause mortality, mortality related to cardiovascular disease, stroke, respiratory disease and Gram-negative bacteraemia all being reported.[51-53] In the majority of cases AKI does not represent intrinsic renal disease but occurs as a result of dysfunction of other organs leading to septic, ischaemic or toxic insults to the kidneys. Although without additional clinical information our dataset does not shed light on the cause of death, it is likely that the seasonal trends in mortality reflect different patterns of mortality associated with the primary underlying diseases which precipitate AKI.

In summary we report for the first time in a large national cohort, a seasonal variation in the incidence and outcomes of AKI. The results demonstrate distinct trends in the incidence and outcome of AKI. Incidence of AKI fell throughout the four quarters of the calendar year whilst mortality was higher in the quarters of January to March and October to December reflecting well-described excess winter mortality association with numerous primary illnesses which may precipitate AKI. This study was derived from a biochemical dataset. Further studies are therefore needed, in which data on clinical diagnosis and cause of death are captured to provide a detailed understanding of these reported trends.

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DP and OY, collected and collated the data. JH designed the study, collected and analysed the data and produced the figures. GR designed the study and validated the algorithm. JG facilitated data collection. LA contributed to data analysis. 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.

There are no competing interests

## DISCLOSURES

No potential conflicts of interest relevant to this article were reported.

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**Appendix 3.10:** Published work 10 related to this thesis:

Holmes *et al*. (2018) 'Adding a new dimension to the weekend effect: an analysis of a national data set of electronic AKI alerts', QJM: An International Journal of Medicine

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Original paper

ORIGINAL PAPER

# Adding a new dimension to the weekend effect: an analysis of a national data set of electronic AKI alerts

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## Summary

**Background:** Increased mortality related to differences in delivery of weekend clinical care is the subject of much debate.
**Aim:** We compared mortality following detection of acute kidney injury (AKI) on week and weekend days across community and hospital settings.
**Design:** A prospective national cohort study, with AKI identified using the Welsh National electronic AKI reporting system.
**Methods:** Data were collected on outcome for all cases of adult AKI in Wales between 1 November 2013 and 31 January 2017.
**Results:** There were a total of 107 298 episodes. Weekday detection of AKI was associated with 28.8% (26 439); 90-day mortality compared to 90-day mortality of 31.9% (4551) for AKI detected on weekdays (RR: 1.11, 95% CI: 1.08–1.14, $P < 0.001$, HR: 1.16 95% CI: 1.12–1.20, $P < 0.001$). There was no 'weekend effect' for mortality associated with hospital-acquired AKI. Weekday detection of community-acquired AKI (CA-AKI) was associated with a 22.6% (10 356) mortality compared with weekend detection of CA-AKI, which was associated with a 28.6% (1619) mortality (RR: 1.26, 95% CI: 1.21–1.32, $P < 0.001$, HR: 1.34, 95%CI: 1.28–1.42, $P < 0.001$). The excess mortality in weekend CA-AKI was driven by CA-AKI detected at the weekend that was not admitted to hospital compared with CA-AKI detected on weekdays which was admitted to hospital (34.5% vs. 19.1%, RR: 1.8, 95% CI: 1.69–1.91, $P < 0.001$, HR: 2.03, 95% CI: 1.88–2.19, $P < 0.001$).
**Conclusion:** 'Weekend effect' in AKI relates to access to in-patient care for patients presenting predominantly to hospital emergency departments with AKI at the weekend.

## Introduction

Concern about increased mortality related to weekend hospital admission is currently the subject of much debate. The so-called 'weekend effect' describes a greater mortality for patients admitted to hospital at the weekend than patients admitted on weekdays. This effect has been described in large national and international studies of elective,[1] emergency[2,3] and all admissions to hospital,[4,5] although there is evidence to suggest that the weekend effect might be specific to some diagnoses and procedure groups only.[6] To date, it is not clear if a weekend effect extends beyond hospitalized patients. An assumption that excess weekend deaths are the direct result of current

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patterns of work, which have fuelled political debate and the argument for the need for organizational change to increase service provision on weekends, and provide 'expanded seven day services'. Recent studies, however, have suggested that the interpretation of the weekend effect is at least in some part explained by data artefact resultant from inconsistent coding and associated weaknesses in administrative data, which cast doubt on the use of measures such as hospital standardized mortality rates.[7,8] A second concern is the weekend effect may also in part reflect failure to consider the severity of acuity of patients' illness.[9] Finally studies describing stroke outcome, using sophisticated adjustment for case mix found no weekend effect, suggesting insufficient consideration of comorbidity may have contributed to previously reported weekend effects in stroke outcome,[10] and cast doubt that the effect is directly related to medical staffing levels.[11] Of note, studies using specialist clinical databases for specific diseases or clinical departments, which include clinical and physiological data, have found little or no significant difference by day of admission.[10,12]

Acute kidney injury (AKI) is a clinical syndrome characterized by rapid loss of kidney function and is associated with adverse patient outcomes.[13–17] AKI may arise as an isolated problem related to intrinsic kidney disease, however, in the majority of cases, it occurs in the setting of circulatory disturbance associated with severe illness, trauma or surgery. AKI therefore represents a complication of a wide spectrum of acute illness. AKI is estimated to occur in up to 15% of hospitalized patients and up to 60% of critically ill patients.[14,15,18] Based on a presumption that early identification may facilitate appropriate of care and improve patient outcomes, an automated real time e-alert system for AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) 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. Using the electronic AKI alert, we have developed a centralized data collection system to provide a comprehensive characterization of the incidence of AKI identified by an electronic alert and its outcome in Wales.[19–21]

In this manuscript, we have used this data set to evaluate the 'weekend effect' and AKI-associated mortality for all cases of biochemically defined AKI across both hospital and community settings. The use of a creatinine-based definition therefore avoids inconsistencies related to coding and also allows a subjective measure of diseases severity using agreed AKI staging criteria.

## Methods

The study was approved under Service Evaluation Project Registration.

### Electronic reporting of AKI

The previously described (and validated) Welsh electronic AKI reporting system,[19,22] utilizes the Welsh Laboratory Information Management System (InterSystems TrakCare Lab) to automatically compare in real time measured creatinine values on an individual patient against previous results. This generates electronic AKI alerts, derived from a nationally agreed algorithm based on KDIGO AKI criteria.[23]

### Data collection

Data were collected for all cases of adult (≥18 years of age) AKI in Wales between 1 November 2013 and 31 January 2017. The days of the week were divided into two groups: weekdays (monday to friday) and weekends (saturday and sunday). All bank holidays were excluded from analysis. 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 30 days following the AKI alert. To prevent inclusion of known patients receiving renal replacement therapy, alerts transmitted by patients from a renal, renal transplant, or dialysis setting and by patients who had a previous blood test in a dialysis unit were excluded. All patients with AKI who required renal support or specialist intervention in a renal unit, alerted in a non-renal location prior to transfer.

Mortality data were collected from the Welsh Demographic Service.[24]

### Data analysis

All patients for which the first alert was issued during a hospital admission who also had a normal serum creatinine (SCr) value generated in a hospital setting within the preceding 7 days were defined as hospital-acquired AKI (HA-AKI). Patients alerting in a non-inpatient setting (including Accident and Emergency/Acute assessment units) or alerting in primary care were classified community-acquired AKI (CA-AKI). About 13 704 AKI episodes occurred in an inpatient setting but no results were available for the previous 7 days and it was not possible to confidently classify these as either CA- or HA-AKI and these were excluded from the subgroup analyses. Hospitalization of CA-AKI (admitted CA-AKI) was defined as a measurement of renal function in a hospital setting within 7 days following the AKI e-alert. About 13 478 (12.6%) patients whilst alerting in an in-patient setting had no results for the previous 7 days. As these patients did not therefore fall into either CA- or HA-AKI definitions, they were designated as undetermined in hospital alerts, but excluded from the subgroup analysis.

An incident AKI episode was defined as 30 days, i.e. any AKI e-alert for the same patient within 30 days the incident alert was not considered a new episode. Pre-existing chronic kidney disease was defined as an estimated Glomerular Filtration (eGFR) (calculated by Chronic Kidney Disease Epidemiology Collaboration (CKDEpi) eGFR formula[25]) $<60\,ml^{-1}\ min^{-1}\ 1.73\ m^2$ derived from the baseline SCr. Admission to was defined as a blood test taken in an Intensive Care Unit (ICU) setting within 7 days of the alert.

Statistical significance was determined by one-way ANOVA, student's t-test and $\chi^2$ test as appropriate. The influence of age, sex and pre-existing CKD on AKI incidence was assessed by logistics regression analysis. P values $< 0.05$ were considered statistically significant.

## Results

### Weekday vs. weekend detection: 90-day mortality

Analyses included a total of 107 298 episodes of AKI in 77 795 patients. Substantially fewer episodes of AKI were detected on weekends than on weekdays (Table 1). Average daily weekday AKI incidence represented 17.3% of the weekly total compared to the average daily weekend incidence of 6.7% ($P < 0.001$). Mortality data were available for 106 227 AKI episodes, in which there were 30 990 (29.2%) deaths within 90 days of the AKI episode. About 26 439 (28.8%) patients in whom AKI was detected on a weekday died within 90 days of the AKI episode, compared

**Table 1.** Comparison of patients for which AKI was detected on a weekend vs. on a weekday[a]

| Variable | All | Weekend | Week | P value weekend vs. week |
|---|---|---|---|---|
| Number of episodes, (average percentage of weekly total occurring per day) | 107 298 | 14 393 (6.7) | 92 905 (17.3) | P<0.001 |
| Mean age ±SD (years) | 71.1 ±17.0 | 70.5 ±17.4 | 71.2 ±17.0 | P<0.001 |
| Males, n (%) | 50159 (46.7) | 7014 (48.7) | 43145 (46.4) | P = n/s |
| Pre existing CKD, n (%) | 36 070 (33.7) | 4660 (32.4) | 31 410 (33.9) | P = n/s |
| AKI severity/stage | | | | |
| Stage 1, n (%) | 82 782 (77.2) | 11 059 (76.8) | 71 723 (77.2) | P = n/s |
| Stage 2, n (%) | 15 791 (14.7) | 2199 (15.3) | 13 592 (14.6) | |
| Stage 3, n (%) | 8725 (8.1) | 1135 (7.9) | 7590 (8.2) | |
| Hospital acquired, n (%, ave. % of weekly total occurring per day) | 41 794 (39.0, n/a) | 6255 (43.5, 7.5) | 35 539 (38.3, 17.0) | P<0.001 |
| Community acquired, n (%, ave. % of weekly total occurring per day) | 52 026 (48.5, n/a) | 5698 (39.6, 5.5) | 46 328 (49.9, 17.8) | P<0.001 |
| Undetermined in hospital alerts, n (%) | 13 478 (12.6) | 2440 (17.0) | 11 038 (11.9) | P<0.001 |
| 90-day mortality, n (%) | 30 990 (28.8) | 4551 (31.9) | 26 439 (28.8) | P<0.001 |

[a]Baseline eGFR data were missing for 260 episodes (255, Week; 5, Weekend) and excluded from analysis of the pre-existing CKD variable. Mortality data were available for 106 227 episodes (91 952, week; 14 275, weekend).

to 4551 (31.9%) patients in whom AKI was detected on a weekend (RR: 1.11, 95% CI: 1.08–1.14, P < 0.001, by linear regression HR: 1.16, 95% CI: 1.12–1.20, P < 0.001). There were no differences in patient demographics in terms of sex or pre-existing CKD between the weekday and weekend groups, although the weekend cohort was marginally younger. Severity of AKI as assessed by AKI stage at detection was no different between the two groups.

## Hospital-acquired AKI

***HA-AKI accounted for 41 794 AKI episodes (39.0%)***

For HA-AKI, the average daily weekday AKI incidence represented 17.0% of the weekly total compared to the average daily weekend incidence of 7.5% of the weekly incidence (P < 0.001). There was no 'weekend effect' for mortality associated with HA-AKI (Table 2); 90-day mortality associated with HA-AKI detected on the weekend represents 2131 patient deaths (34.4%) compared with 12 523 deaths (35.5%) in HA-AKI detected on a weekday. There were no differences in patient demographics in terms of sex or pre-existing CKD between the weekday and weekend HA-AKI groups, although the weekend cohort was significantly younger. Severity of illness as assessed by AKI stage at presentation was no different in those presenting on a weekend (AKI1: 83.9%, AKI2/3; 16.1%) compared to a weekday (AKI1: 82.7%, AKI2; 17.3%). The same pattern was also seen in the undetermined in hospital alerts (Supplementary Table S1).

**Table 2.** Comparison of hospital-acquired AKI patients for which AKI was detected on a weekend vs. on a weekday[a]

| Variable | Weekend | Week | P value |
|---|---|---|---|
| Number of episodes (percenatge of all episodes, average percentage of weekly total occurring per day) | 6255 (15, 7.5) | 35 539 (85, 17.0) | P < 0.001 |
| Mean age ±SD (years) | 72.2 ±16.6 | 74 ±15.8 | P < 0.001 |
| Males, n (%) | 3119 (49.9) | 16 716 (47.0) | P = n/s |
| Pre existing CKD, n (%) | 2191 (35.0) | 12 188 (34.3) | P = n/s |
| AKI severity/stage | | | |
| Stage 1, n (%) | 5251 (83.9) | 29 375 (82.7) | P = n/s |
| Stage 2, n (%) | 731 (11.7) | 4448 (12.5) | |
| Stage 3, n (%) | 273 (4.4) | 1716 (4.8) | |
| 90-day mortality, n (%) | 2131 (34.4) | 12 523 (35.5) | P = 0.07 |

[a]Baseline eGFR data weres missing for 29 episodes (27, week; 2, weekend) and excluded from analysis of the pre-existing CKD variable. Mortality data were available for 41 434 episodes (35 234, week; 6200, weekend).

## Community-acquired AKI

***CA-AKI accounted for 52 016 (48.5%) AKI episodes***

CA-AKI detected at the weekend was associated with a significantly higher 90-day mortality (Table 3). Weekday detection of AKI was associated with a 22.6% (10 356) mortality compared with weekend detection of AKI which was associated with a 28.6% (1619) mortality (RR: 1.26, 95% CI: 1.21–1.32, P < 0.001, by regression HR: 1.34, 95% CI:1.28–1.42, P < 0.001). There were no differences in patient demographics in terms of age, sex or pre-existing CKD between the weekday and weekend CA-AKI groups. At the weekend, there was a significantly higher proportion of AKI 2/3 (28.5%) compared to weekdays (15.6%, P < 0.001). By Cox regression AKI stage 2/3 was associated with higher hazard of death (AKI 2/3 vs. AKI 1; HR: 2.15, 95% CI: 2.07–2.23,

Table 3. Comparison of all, admitted and non-admitted community-acquired AKI patients for which AKI was detected on a weekend vs. on a weekday[a]

| Variable | CA-AKI | | | | Admitted CA-AKI | | | | Non-admitted CA-AKI | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | Weekend | Week | P value, weekend vs. week | All | Weekend | Week | P value, weekend vs. week | All | Weekend | Week | P value, weekend vs. week |
| Number of episodes | 52 026 | 5698 | 46 328 | | 21 067 | 3494 | 17 573 | | 30 959 | 2204 | 28 755 | |
| Mean age ±SD (yrs) | 69.5 ±17.7 | 69.8 ±18.2 | 69.5 ±17.6 | P = n/s | 72 ±16.0 | 71.7 ±16.6 | 72.1 ±15.9 | P = n/s | 67.8 ±18.5 | 66.9 ±20.1 | 67.9 ±18.4 | P = 0.02 |
| Males, n (%)Pre existing CKD, n (%) | 23499 | 2622 | 20877 | P = n/s | 10353 | 1652 | 8701 | P = n/s | 13 146 | 970 | 12176 | P = n/s |
| | (45.2) | (46.0) | (45.1) | | (49.1) | (47.3) | (49.5) | | (42.5) | (44.0) | (42.3) | |
| | 17 559 | 1727 | 15 832 | P = n/s | 8299 | 1191 | 7108 | P = n/s | 9260 | 536 | 8724 | P = n/s |
| | (33.9) | (30.3) | (34.3) | | (39.4) | (34.1) | (40.5) | | (30.1) | (24.3) | (30.5) | |
| AKI severity/stage | | | | | | | | | | | | |
| Stage 1, n (%) | 38543 | 4075 | 34468 | P<0.001 | 13564 | 2383 | 11 181 | P<0.001 | 24 979 | 1692 | 23 287 | P<0.001 |
| | (74.1) | (71.5) | (74.4) | | (64.4) | (68.2) | (63.6) | | (80.7) | (76.8) | (81) | |
| Stage 2, n (%) | 8237 | 1044 | 7193 | | 4417 | 719 | 3698 | | 3820 | 325 | 3495 | |
| | (15.8) | (18.3) | (15.5) | | (21.0) | (20.6) | (21.0) | | (12.3) | (14.7) | (12.2) | |
| Stage 3, n (%) | 5246 | 579 | 4667 | | 3086 | 392 | 2694 | | 2160 | 187 | 1973 | |
| | (10.1) | (10.2) | (10.1) | | (14.6) | (11.2) | (15.3) | | (7.0) | (8.5) | (6.9) | |
| Mean time to repeat test ±SD (days) | 8.4 ±15.1 | 4.3 ±11.2 | 9.0 ±15.4 | P<0.001 | 1.3 ±1.2 | 1.3 ±1.1 | 1.3 ±1.3 | P = n/s | 15.6 ±18.7 | 12.7 ±19.4 | 15.8 ±18.7 | P <0.001 |
| 90-day mortality, n (%) | 11975 | 1619 | 10356 | P<0.001 | 5797 | 863 | 4934 | P<0.001 | 6178 | 756 | 5422 | P<0.001 |
| | (23.3) | (28.6) | (22.6) | | (27.7) | (24.8) | (28.2) | | (20.2) | (34.5) | (19.1) | |

[a]Baseline eGFR data were missing for 203 CA-AKI episodes (202, week; 1, weekend), 27 admitted CA-AKI episodes (26, week; 1, weekend) and 176 non-admitted CA-AKI episodes (176, week; 0, weekend) and excluded from analysis of the pre-existing CKD variable. Mortality data were available for 51 472 CA-AKI episodes (45 0805, week; 5667, weekend), 20 958 admitted CA-AKI episodes (17 482, week; 3476, weekend) and 30 514 non-admitted CA-AKI episodes (28 323, week; 2191, weekend).

$P < 0.001$). Weekend CA-AKI-associated mortality adjusted for AKI stage remained associated with a higher hazard of death compared to weekday CA-AKI (HR: 1.31, 95% CI: 1.25–1.38, $P < 0.001$).

### Hospitalized CA-AKI

CA-AKI was associated with hospital admission in 42% of episodes (Table 3). Mortality for CA-AKI detected during the week and subsequently admitted to hospital (Table 3) was associated with a higher 90-day mortality (28%) than CA-AKI detected during the weekend (24.8%) and admitted to hospital (RR week vs. weekend: 1.14 95% CI: 1.07–1.21, $P < 0.001$). Severity of illness assessed by AKI stage at presentation was greater for admitted CA-AKI detected on weekdays (AKI1: 63.6%, AKI2/3; 36.4%) compared to admitted CA-AKI detected at the weekend (AKI1: 68.2%, AKI2/3 31.8%, $P < 0.001$). By Cox regression weekday CA-AKI-associated mortality in the admitted cohort, adjusted for AKI stage remained weakly associated with a higher hazard of death (HR week vs. weekend: 1.08, 95% CI: 1.01–1.15, $P = 0.02$). Within this group of admitted CA-AKI, 98% had a repeat measurement of renal function in a ward setting within an average of 36 h suggesting that these patients were admitted on the day of AKI detection (i.e. weekend admission).

### Non-admitted CA-AKI

Non-admission of CA-AKI detected at the weekend (Table 3) was associated with a significantly higher mortality than non-admission of CA-AKI detected on weekdays (34.5% vs. 19.1%, RR: 1.8, 95% CI: 1.69–1.91, $P < 0.001$, HR: 2.07, 95% CI: 1.92–2.24, $P < 0.001$). The proportion of all CA-AKI detected at hospital, increased at the weekend compared to CA-AKI detected at a hospital setting on a weekday (96.2% vs. 64.8%, $P < 0.001$). At the weekend, the proportion of CA-AKI admitted to hospital was also significantly higher compared to weekday AKI (61.3% vs. 39.9%, $P < 0.001$). There was however a greater proportion of AKI stages 2 and 3 in the CA-AKI non-admitted patients in whom AKI was detected at the weekend (weekend AKI 2/3; 23.2% vs. weekday AKI 2/3, 10.0%, $P < 0.001$). Weekend AKI-associated mortality, adjusted for AKI stage, in non-admitted CA-AKI, however, remained associated with a higher hazard of death compared to the weekday group of CA-AKI who were not admitted (HR: 2.03, 95% CI: 1.88–2.19, $P < 0.001$).

For CA-AKI patients who are not admitted to hospital we have previously reported that a significant proportion of patients have no repeat measurement of renal function and that the time to repeat for those who do have a check of renal function is significantly delayed. The adverse effects of weekend detected CA-AKI in the non-admitted group could not however be explained by differences in follow-up care. The proportion of those with repeat blood test was significantly higher in non-admitted CA-AKI weekend AKI compared to the non-admitted CA-AKI weekday patients (34.3% vs. 31.3%, $P = 0.004$). In addition, for those who did have a repeat measurement of renal function the time to repeat was significantly less in the weekend CA-AKI non-admitted group ($5.7 \pm 7.2$ days vs. $8.8 \pm 7.7$ days, $P < 0.001$).

## Discussion

There are little published data addressing the weekend effect in AKI, with published data focused only on patients hospitalized with AKI in which weekend admission was associated with a higher risk for death compared to admission on a weekday.[26] Using a data set of over 100 000 episodes of AKI, we have described the variation in mortality across both hospital- and community-based services. The study demonstrates that AKI detected at the weekend is associated with increased risk of death within 90 day of the AKI episode. Whilst this effect is apparent across all cases of AKI closer scrutiny of the data demonstrates that this effect is driven by the excess mortality associated with AKI detected in the community which is not admitted to hospital. Within this cohort, it is significant that there is a higher proportion of AKI stages 2 and 3, which predominantly present to hospital emergency departments where their AKI is highlighted by an electronic alert, but who are subsequently discharged to the community. Previously, we have demonstrated that poor outcome for non-admitted CA-AKI is associated with inadequate follow-up in terms of measuring renal function.[19,20] This study confirms that a significant proportion of CA-AKI who are not admitted to hospital have no further measurement of renal function and for those who do have a subsequent measure of renal function following reporting of AKI, there is a significant delay. These deficiencies however, apply equally to non-admitted CA-AKI detected on weekdays and weekends.

In contrast, AKI acquired in hospital or in the community and admitted to hospital does not demonstrate this 'weekend effect' of excess mortality. Furthermore, for patients with CA-AKI who are admitted, weekend detection and admission of AKI is associated with improved mortality. These data therefore demonstrate that a weekend effect in AKI is not a reflection of the quality of in-hospital care. These observations are consistent with data demonstrating similar outcomes for severe AKI when dialysis was initiated on sundays compared to initiation on other days of the week,[27] and a recent propensity score matched, population-based study work demonstrating that weekend admission in patients with severe AKI requiring dialysis had no effect on patient mortality.[28]

Whilst many studies have confirmed excess mortality associated with the 'weekend effect', concern has been expressed regarding interpretation of the cause of these reported observations.[29,30] Criticism of interpretation of previous published studies describing the 'weekend effect' highlights issues related to coding inaccuracies and objective measures of disease severity. A strength of our study is its accuracy and is not dependent on coding but rather on objective measureable changes in SCr. The diagnostic criteria for AKI are based on internationally accepted definitions which also allow staging of AKI severity based on the magnitude of the changes in creatinine thus providing a direct and objective measure of disease severity.

The use of a national data set that collect data on every episode also allows capture of data across the whole of the health community and therefore includes information on both hospitalized and patients 'managed' in the community. This approach therefore allows us to examine the interface between community and hospital services. This approach highlights a novel aspect of the 'weekend effect' as the disparity in patient mortality is highest in patients diagnosed with AKI predominantly at the hospital 'front door' at the weekend but who are not admitted to hospital.

Although this study uses a novel approach to address the 'weekend effect', it is limited by the use of a biochemistry based data set. The data therefore lack clinical context beyond the presence of pre-existing CKD, the detail of the cause of AKI and the cause of death. In addition as the data lack information regarding co-morbidities or medication exposure as it is

therefore not possible from our data set to determine their contribution to the higher weekend-associated mortality. In addition, there is no linkage to primary care data sets and therefore the clinical response cannot be captured. Finally, the diagnosis of AKI is made by comparing measured creatinine values on an individual patient against the patients' previous results, to generate alerts. This approach does consequently precludes the inclusion of the first presentation of AKI in a patient with no previous blood test on the system. This is however to our knowledge the first multicentre national study using a biochemical-based reporting system to describe the weekend effect associated AKI.

The results suggest that the 'weekend effect' in AKI not associated with quality of care but access to care. The lack of effect of weekend detection of AKI on patient mortality for admitted CA-AKI and improved outcome for HA-AKI suggest no inequity of hospital based care at the weekend and therefore unlikely to be related to current models of medical staffing. In contrast, the study suggests that AKI-associated weekend effect relate to changing patterns of admission for CA-AKI at the weekend. This is consistent with previous studies that suggest a higher accident and emergency admission threshold at weekends.[9] Possible explanations for this include an inappropriate delay in hospital discharge at weekends leading to pressure on in-patient beds[31] and reduced availability of primary care services[9] resulting in a greater proportion of CA-AKI presenting directly to hospitals at the weekend. Recent data suggest that a 7-day team-based model of care improves patient flow and weekend discharges[32] and increased access to primary care, which significantly reduces the weekend workload in A&E departments.[33]

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J.H. designed the study, collected and analyzed the data and produced the figures. J.D.W., T.R. and J.G. interpreted the data and wrote the report. A.O.P. set up the program of work, designed the study, interpreted the data and wrote the report.

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## Supplementary material

Supplementary material is available at *QJMED* online.

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*Conflict of interest*: None declared.

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**Appendix 3.11:** Published work 11 related to this thesis:

Holmes *et al*. (2020) 'Recurrent acute kidney injury: predictors and impact in a large population-based cohort', Nephrology Dialysis Transplantation

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020; 3: e208857
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# Recurrent acute kidney injury: predictors and impact in a large population-based cohort

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## ABSTRACT

**Background.** This study examined the impact of recurrent episodes of acute kidney injury (AKI) on patient outcomes.

**Methods.** The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients ≥18 years of age between April 2015 and September 2018. Patients were grouped according to the number of AKI episodes they experienced with each patient's first episode described as their index episode. We compared the demography and patient outcomes of those patients with a single AKI episode with those patients with multiple AKI episodes. Analysis included 153 776 AKI episodes in 111 528 patients.

**Results.** Of those who experienced AKI and survived their index episode, 29.3% experienced a second episode, 9.9% a third episode and 4.0% experienced fourth or more episodes. Thirty-day mortality for those patients with multiple episodes of AKI was significantly higher than for those patients with a single episode (31.3% versus 24.9%, $P < 0.001$). Following a single episode, recovery to baseline renal function at 30 days was achieved in 83.6% of patients and was significantly higher than for patients who had repeated episodes (77.8%, $P < 0.001$). For surviving patients, non-recovery of renal function following any AKI episode was significantly associated with a higher probability of a further AKI episode (33.4% versus 41.0%, $P < 0.001$). Furthermore, with each episode of AKI the likelihood of a subsequent episode also increased (31.0% versus 43.2% versus 51.2% versus 51.7% following a first, second, third and fourth episode, $P < 0.001$ for all comparisons).

**Conclusions.** The results of this study provide an important contribution to the debate regarding the need for risk stratification for recurrent AKI. The data suggest that such a tool would be useful given the poor patient and renal outcomes associated with recurrent AKI episodes as highlighted by this study.

**Keywords:** acute kidney injury, CKD, CKD-EPI equation, epidemiology, survival analysis

## INTRODUCTION

Acute kidney injury (AKI) is associated with increased patient morbidity and mortality [1, 2]. While in-hospital consequences of AKI are well-described, consequences beyond the index event are less well-characterized. Based on a presumption that early identification may help raise standards of care and improve patient outcomes, an automated real-time electronic (e)-alert system for AKI based on the Kidney Disease: Improving Global Outcomes (KDIGO) change in creatinine diagnostic criteria has been implemented nationally across all areas of the National Health Service (NHS) in England and Wales. Using the e-AKI alert, we have developed a centralized data collection system to provide a comprehensive characterization of the incidence and outcomes of AKI identified by an e-alert in Wales, United Kingdom [3–5].

Previous data suggest that AKI is associated with higher rates of re-hospitalization, with up to 20% of patients readmitted within 30 days [6]. Relatively few studies, however, have described the epidemiology of recurrent AKI. In the largest study to date, Liu *et al.* [7] in a study of 38 659 patients who experienced a hospitalized episode of AKI, identified a second AKI episode in 28.6% of patients. This is similar to that reported by Siew *et al.* [8] demonstrating a 25% recurrence rate for AKI within 12 months of discharge. The latter study, however, described cases from a regional Veterans Administration database and therefore focused predominantly on a hospitalized male patient cohort. Other studies addressing recurrent AKI are relatively small in patient numbers [9, 10], or focus on specific patient cohorts [11, 12]. The aims of this study were to determine the incidence and outcomes of repeated episodes of AKI and identify potential risk factors for recurrence from a large population-based data set.

## MATERIALS AND METHODS

This case series study used the Welsh National e-alerting system for AKI to identify all cases of AKI in patients over the age of 18 years between April 2015 and September 2018. The Medical Record Number, a unique reference number allocated to patients registered in the National Laboratory Information Management System, was used as the patient identifier. The study has been approved under the conditions of 'Service Evaluation Project Registration'.

The e-alerting system generates alerts by comparing a current creatinine value to historic creatinine measurements for the same patient in real time. It defines AKI according to KDIGO increase in creatinine parameters [3]. An AKI episode was defined as a period of 30 days. Any AKI e-alert for the same patient within 30 days of the initial alert was not considered a new episode. The first AKI episode was defined as the index episode. To examine the impact of recurrent episodes, patients were classified as either having one episode, two episodes, three episodes, or four or more episodes.

To avoid spurious results resultant from fluctuations in creatinine related to renal replacement therapies, dialysis patients, patients with a known renal transplant and alerts generated in renal ward settings were excluded from the analysis [3].

In addition to measurements of renal function, data were collected on patient age, gender, stage of index AKI episode, pre-existing chronic kidney disease (CKD) [estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration eGFR equation [13] and pre-existing CKD was defined as an eGFR $<60$mL/min per 1.73 $m^2$ derived from the baseline serum creatinine (SCr) associated with the index episode], and the clinical location at which the index episode was generated. An episode was defined as hospital-acquired (HA)-AKI if the initial alert was transmitted by a blood test request in an inpatient or intensive therapy unit (ITU) and high dependency setting. All other episodes were defined as community-acquired (CA)-AKI.

Data on patient mortality were collected from the Welsh Demographic Service [14]. Recovery was defined as achievement of a SCr value during the episode no longer in keeping with the definition of AKI when compared with the baseline SCr value associated with the episode. Patients were only included in the recovery analysis if they survived their episode and had at least one SCr test during the episode. Socio-economic classification of patients was derived from the Welsh Index of Multiple Deprivation (WIMD) score [15]. This is the Welsh Government's official measure of relative deprivation in which the population of Wales is divided into 1909 geographical units called lower super output areas (LSOAs) each with an average population of 1600 people. The WIMD score is constructed from a weighted sum of the deprivation score for each of the following domains: income (23.5%), employment (23.5%), health (14.0%), education (14.0%), access to services (10.0%), community safety (5.0%), physical environment (5.0%) and housing (5.0%). Patients were grouped according to the WIMD score by their postcode and corresponding LSOA of residence, and the ranked data were categorized into percentiles, with percentile 1 being the most socio-economically deprived and percentile 100 being the least deprived.

Statistical analysis was carried out using SPSS software, version 25 (IBM SPSS, Chicago, IL, USA). Student's *t*-test was used for analysis of normally distributed data. Categorical data were compared using a Pearson chi-squared test. Kaplan–Meier analysis was used to estimate and compare survival of patient groups. Binomial logistic regression was used to understand whether 30-day AKI-associated mortality, and recovery from an AKI episode, can be predicted by the number of episodes incurred by a patient. We did this analysis both unadjusted and adjusted for patient demographic covariates, which included pre-existing CKD, AKI stage of index episode, AKI type of index episode, gender and age. $P<0.05$ were considered statistically significant. For binomial data, 95% confidence intervals were defined as 1.96 multiplied by the standard error.

Data were collected from all Health Boards in the NHS in Wales, representing a population of 3.06 million people. A total of 153 776 episodes of AKI in 111 528 patients were identified. Average follow-up time for index episodes was $448.5 \pm 401.4$ days with a median of 349.3 days. Details of cohort creation are shown in Figure 1.

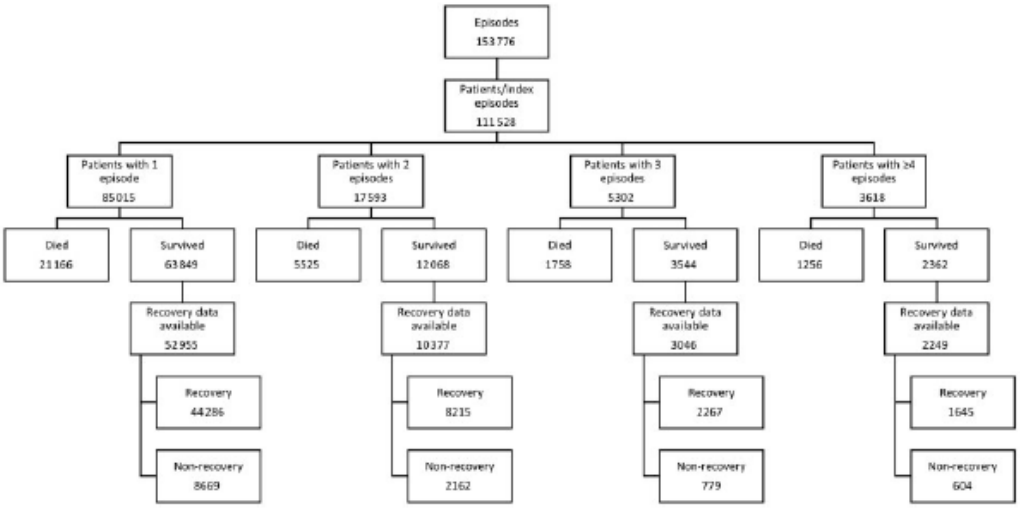


FIGURE 1: Flow diagram of cohort creation, with exclusion and inclusion criteria.

**Table 1. Demography of patients with one AKI episode, two AKI episodes, three AKI episodes and four or more AKI episodes**

| | One episode | Two episodes | Three episodes | Four or more episodes |
|---|---|---|---|---|
| Number of patients, *n* (% of all patients) | 85 015 (76.2) | 17 593 (15.8) | 5302 (4.8) | 3618 (3.2) |
| Mean age ± SD at index episode, year | 70.49 ± 17.9 | 73.22 ± 15.1 | 71.84 ± 14.84 | 67.94 ± 15.49 |
| Gender, % (*n*) | | | | |
| Male | 46.3 (39 353) | 47 (8428) | 49.8 (2638) | 47.9 (1732) |
| Female | 53.7 (45 662) | 52.1 (9165) | 50.2 (2664) | 52.1 (1886) |
| Pre-existing CKD, % (*n*) | 28.8 (24 493) | 35.6 (6260) | 33.3 (1932) | 31.1 (1125) |
| AKI stage of index episode, % (*n*) | | | | |
| Stage 1 | 78.2 (66 446) | 79.2 (13 936) | 79.7 (4224) | 79.9 (2891) |
| Stage 2 | 14.5 (12 378) | 13.3 (2335) | 12.4 (655) | 12.5 (452) |
| Stage 3 | 7.3 (6191) | 7.5 (1322) | 7.9 (423) | 7.6 (275) |
| Type of AKI at index episode, % (*n*) | | | | |
| CA-AKI | 50.9 (43 286) | 51.7 (9086) | 51.4 (2724) | 49.1 (1777) |
| HA-AKI | 49.1 (41 729) | 48.3 (8507) | 48.6 (2578) | 50.9 (1841) |
| Specialty of AKI at index episode, % of HA (*n*) | | | | |
| General medicine | 22.8 (9501) | 24.3 (2071) | 23.0 (593) | 21.7 (399) |
| General surgery | 13.0 (5427) | 12.8 (1091) | 13.9 (357) | 17.1 (314) |
| Trauma and orthopaedic | 9.2 (3855) | 8.1 (782) | 6.5 (168) | 5.7 (104) |
| Cardiology | 7.5 (3137) | 9.2 (782) | 9.8 (252) | 8.9 (164) |
| ITU and high dependency | 10.1 (4232) | 9.0 (766) | 10.4 (269) | 12.3 (227) |
| Mean WIMD percentile ± SD | 47.91 ± 28.32 | 47.41 ± 28.15 | 46.20 ± 27.96 | 46.06 ± 28.11 |

## RESULTS

### Patient characteristics

The distribution of AKI severity for the index episode was AKI1 78.4%, AKI2 14.2% and AKI3 7.4%. The mean age of the whole cohort was 70.91 ± 17.3 years. Fifty-three per cent of the AKI patients were female. Pre-existing CKD was identified in 28.3%. A total of 50.99% cases were HA-AKI and 49.01% CA-AKI.

Of those who experienced AKI and survived the index episode, 29.3% (26 513) experienced a second episode, 9.9% (8920) a third episode and 4.0% (3618) experienced fourth or more episodes. In total, this represents 68 761 recurrent AKI episodes. The second episode occurred a mean of 231 ± 358 days following the first episode, the third episode a mean of 169 ± 184 days following the second, and the fourth a mean of 134.8 ± 145 days following the third episode. Patient demographics and location of the index episode are shown in Table 1.

### Patient demographics associated with recurrent AKI

Patients experiencing recurrent AKI were significantly older than those who had a single episode (two or more episodes 72.22 ± 15.2 years versus one episode 70.49 ± 17.9 years, $P < 0.001$). For those patients with repeated episodes, those who experienced two episodes were significantly older (73.22 ± 15.08 years) than those who experienced three episodes (71.84 ± 14.85 years, $P < 0.001$), who were in turn

significantly older than those who experienced four or more episodes (67.94 ± 15.49 years, P < 0.001). In those surviving the first AKI episode, a higher proportion of male patients experienced recurrent episodes of AKI (two or more episodes: male 29.6% versus female 25.9%, P < 0.001).

A higher percentage of patients with repeated episodes of AKI had pre-existing CKD compared with those who experienced only one episode (two or more episodes 35.1% versus one episode 28.8%). There was also a significantly higher percentage of pre-existing CKD in patients who experienced two (35.6%) or three (33.3%) recurrent episodes compared with those who experienced four or more episodes (31.1%, P < 0.001).

The severity of the index AKI episode was assessed by AKI stage at presentation. There were significantly more Stage 1 index episodes for patients who had multiple episodes, compared to patients who had a single episode (one episode: Stage 1 = 78.2%, Stage 2 = 14.6%, Stage 3 = 7.3%; two or more episodes: Stage 1 = 79.4%, Stage 2 = 13.0%, Stage 3 = 7.6%, P < 0.001).

For surviving patients with biochemistry data available on renal outcome, non-recovery of renal function following any AKI episode was associated with a higher probability of a further AKI episode (33.4% versus 41.0%, P < 0.001). Furthermore, with each episode of AKI, the likelihood of another subsequent episode also increased (Figure 2). If renal function returned to baseline, the likelihood of at least one further episode of AKI rose from 30.1% following the first episode to 48.3% following four AKI episodes. If renal function did not recover to baseline, the likelihood of at least one further episode of AKI rose from 35.3% following the first episode to 59.7% following four AKI episodes.

Recurrent episodes of AKI were more common following an index case of HA-AKI compared with an index case of CA-AKI. Location of the index episode did not influence the likelihood of a recurrent episode. Figure 3 shows the full patient journey for patients who had multiple episodes and highlights that recurrent episodes were more likely to be the same type as their index episodes. A second episode of AKI occurred in 28.9% of patients surviving an index HA-AKI episode compared with 26.4% patients surviving an index CA-AKI episode (P < 0.001). Similarly, compared with CA, more patients surviving an HA index episode had a third episode and fourth or more episodes (three episodes: 7.9% versus HA-AKI 8.8%, P < 0.001; four or more episodes: 5.2% versus HA-AKI 6.3%, P < 0.001). To assess the association between recurrent AKI and social deprivation we looked at the mean WIMD score

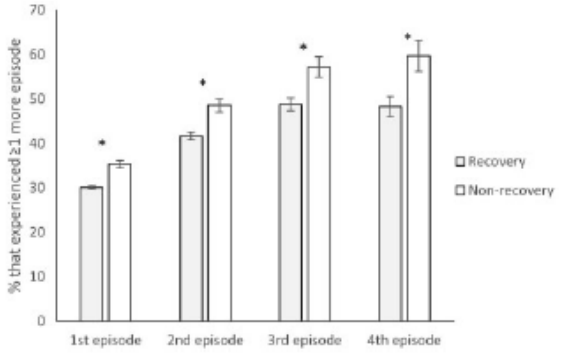


FIGURE 2: The impact of renal recovery of AKI episodes on the probability of recurrent AKI episodes. A total of 76 744 patients survived and had recovery data available for their index (first) episode (63 349, recovery; 13 395, non-recovery), 19 063 of those that recovered had a second episode and 4726 of those that did not recover had a second episode; 18 282 patients survived and had recovery data available for their second episode (14 078, recovery; 4204, non-recovery), 5863 of those that recovered had a third episode and 2041 of those that did not recover had a third episode; 6245 patients survived and had recovery data available for their third episode (4425, recovery; 1820, non-recovery), 2158 of those that recovered had a fourth episode and 1041 of those that did not recover had a fourth episode; 2635 patients survived and had recovery data available for their fourth episode (1859, recovery; 776, non-recovery), 898 of those that recovered had a further episode and 463 of those that did not recover had a further episode. Error bars represent 95% confidence intervals. Asterisks represent statistically significant differences.

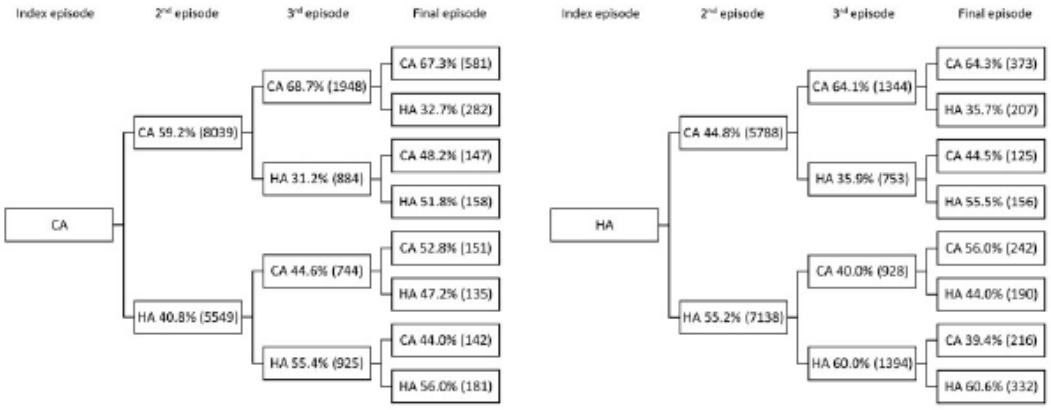


FIGURE 3: Flow diagram of patient journey for patients with multiple episodes. A total of 26 514 patients had more than one episode and were included in the analysis (13 588, CA; 12 926, HA).

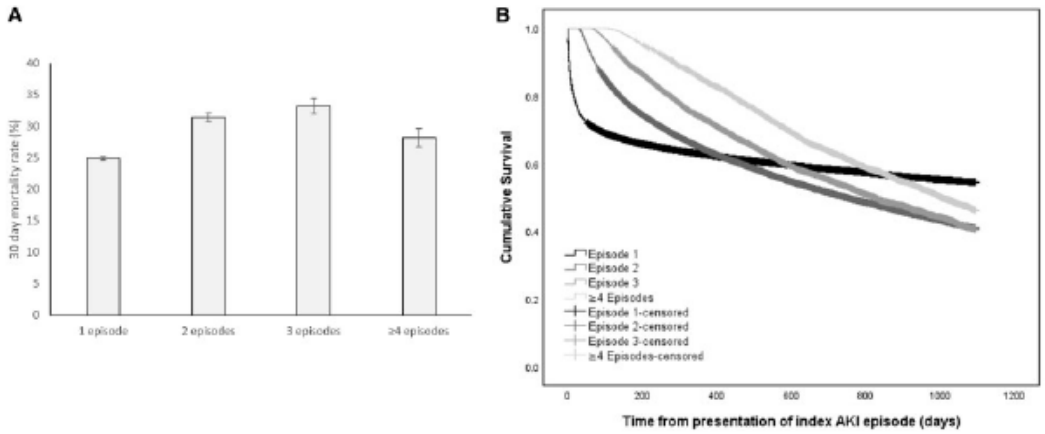


**FIGURE 4:** The impact of recurrent episodes of AKI on 30-day mortality and patient survival. **(A)** Thirty-day mortality rates for patients with one AKI episode, two AKI episodes, three AKI episodes and four or more AKI episodes. Mortality data were available for 111 528 patients (85 015, one episode; 17 953, two episodes; 5302, three episodes; 3618, four or more episodes). **(B)** Kaplan–Meier survival curves for patients with one AKI episode, two AKI episodes, three AKI episodes and four or more AKI episodes. Error bars represent 95% confidence intervals.

where a lower WIMD score corresponds to a higher level of social deprivation. Recurrent AKI was associated with greater social deprivation as the mean WIMD score was significantly lower for patients with recurrent AKI episodes (WIMD score 46.9 ± 28.0) compared with those with a single AKI episode (WIMD score 47.9 ± 28.3 $P < 0.001$).

### Significance of AKI

**Mortality.** Thirty-day mortality following a single episode of AKI was 24.9% (Figure 4A). Repeated episodes of AKI (i.e. two or more episodes) were associated with significantly higher 30-day mortality (31.3%) than a single episode ($P < 0.001$). Thirty-day mortality was also significantly higher for patients who experienced two (31.4%) or three (33.6%) episodes compared with those who experienced four or more episodes (28.2%) of AKI ($P < 0.001$). Kaplan–Meier curves (censored at 3 years of follow-up) showing survival depending on the number of AKI episodes are in Figure 4B. Censored survival was significantly better for patients who had a single episode of AKI compared with multiple episodes ($P < 0.001$), but was not significantly different for patients who experienced two, three or four or more episodes. Overall mortality with a maximum follow-up time of 1330 days was 24.9% for patients with one episode and 31.3% for patients with multiple episodes. This is in comparison with the age-standardized mortality rate for Wales of 1035.6 per 100 000 population [14].

Table 2 shows that males were significantly more likely to experience death within 30 days compared with females. Moreover, the likelihood of death increased significantly with age, if a patient had pre-existing CKD, and if the index episode was HA and Stage 3. Binary logistic regression also showed that for patients who experienced two episodes, the odds of dying within 30 days were 38% [odds ratio (OR) = 1.38, $P < 0.001$] higher than for patients who experienced just one episode, 50% (OR = 1.50, $P < 0.001$) for three episodes and 18% (OR = 1.18, $P < 0.001$) for four or more. The adjusted values in Table 2 show that when adjusted for all other variables, the odds of death increased for all groups except those patients with two episodes.

**Thirty-day renal outcome.** For each AKI episode between 14% and 19% of patients had no biochemical data available to assess recovery of renal function and were excluded. Following a single episode, recovery was achieved in 83.6% of patients (Figure 5). This was significantly higher than for patients who had repeated episodes (77.8%, $P < 0.001$). Recovery was also lower for patients who experienced three (74.4%), or four or more episodes (73.9%) compared with patients who experienced only two episodes of AKI (79.2%, $P < 0.001$).

Table 3 shows that males were significantly less likely to recover compared with females. Moreover, the likelihood of recovery increased significantly with age, and if the index episode was HA, and decreased if a patient had pre-existing CKD, and the index episode was Stage 3. Binary logistic regression also showed that for patients who experienced two episodes, the odds of recovering were 26% (OR = 0.75, $P < 0.001$) lower than for patients who experienced just one episode, 43% (OR = 0.57, $P < 0.001$) for three episodes and 46% (OR = 0.54, $P < 0.001$) for four or more. The adjusted values in Table 3 show that when adjusted for all other variables, the odds of recovery increased for all groups.

## DISCUSSION

Previous studies have suggested that AKI is a risk factor for CKD progression [16–18]. Observational studies link the progression of CKD including the development of end-stage renal failure to previous episodes of AKI. Few studies have, however, examined the epidemiology or impact of recurrent episodes of AKI. A study focused on patients with diabetes mellitus suggests that AKI episodes are associated with a cumulative risk for

**Table 2. Adjusted and unadjusted ORs for risk factors in predicting 30 day AKI associated mortality**

| | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P |
| Total number of episodes | | | | |
| 1 | Reference | – | – | – |
| 2 | 1.38 (1.33–1.43) | 0.000 | 1.33 (1.28–1.38) | 0.000 |
| 3 | 1.50 (1.41–1.59) | 0.000 | 1.53 (1.44–1.63) | 0.000 |
| ≥4 | 1.18 (1.10–1.28) | 0.000 | 1.37 (1.27–1.48) | 0.000 |
| Gender | | | | |
| Female | Reference | – | – | – |
| Male | 1.28 (1.25–1.32) | 0.000 | – | – |
| Pre-existing CKD | | | | |
| No | Reference | – | – | – |
| Yes | 1.10 (1.07–1.14) | 0.000 | – | – |
| AKI stage of index episode | | | | |
| Stage 1 | Reference | – | – | – |
| Stage 2 | 1.77 (1.71–1.84) | 0.000 | – | – |
| Stage 3 | 1.91 (1.82–2.01) | 0.000 | – | – |
| AKI type of index episode | | | | |
| CA | Reference | – | – | – |
| HA | 1.61 (1.55–1.66) | 0.000 | – | – |
| Age at index episode, years | 1.04 (1.04–1.04) | 0.000 | – | – |

[a]Adjusted for sex, pre-existing CKD, AKI stage of index episode, AKI type of index episode and age at index episode.
CI, confidence interval.

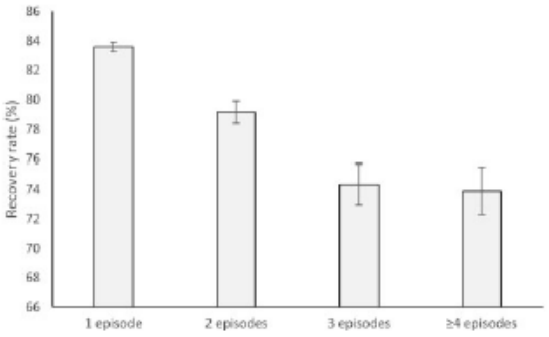


**FIGURE 5:** Recovery of renal function for patients with one AKI episode, two AKI episodes, three AKI episodes and four or more AKI episodes. A total of 82 059 patients survived and had recovery data available (63 849, one episode; 12 068, two episodes; 3544, three episodes; 2598, four or more episodes). Error bars represent 95% confidence intervals.

developing advanced CKD [19], and studies in critically ill patients suggest that recurrent AKI is associated with worse outcomes [10, 12]. A small single-centre retrospective study of only 350 patients surviving AKI suggested that development of CKD was more likely with recurrent AKI [10]. In what is to our knowledge the largest study to date, using a national data set, we have shown that roughly a third of patients who have an episode of AKI will experience at least one further episode and a significant number of patients experience multiple episodes. These data are similar to those of Liu *et al.* in which almost a third of 40 000 hospitalized AKI cases experienced an episode of recurrent AKI during a median follow-up of 1.8 years [7]. Our data are also consistent with the data of Siew *et al.*, drawn from almost 12 000 AKI cases based on a regional Veterans Administration database, in which almost one in eight patients experienced two recurrences [8]. Our study, however, is drawn from >150 000 episodes and it is of note that we have not focused on hospitalized patients and instead used population-based data. We have previously demonstrated that a focus on hospitalized patients with a diagnosis based on retrospective coding data leads to significant under-reporting of AKI compared with e-AKI alerts [3, 4, 20].

The significance of repeated episodes is highlighted by the increase in mortality for patients who experience multiple episodes. This increase in short- and longer term mortality was higher for all cohorts with repeated AKI episodes. Regression analysis also showed that the likelihood of death within 30 days of an AKI episode was higher for patients with recurrent episodes compared with patients with a single episode. While the highest short-term mortality was seen in the groups with either two or three AKI episodes, 30-day mortality in those experiencing four or more episodes remains higher than those experiencing only one episode. Although the group of patients who experience four or more episodes contained >3500 patients, this was the smallest cohort and therefore the lower mortality should be interpreted cautiously. Moreover, it is notable that 30-day mortality does not increase monotonically beyond the third episode of AKI. Rather this could represent survivor selection bias, since to have a fourth episode of AKI, patients have already survived three episodes as is illustrated in the Kaplan–Meier curves. The lack of a stepwise increase in mortality with each recurrent episode of AKI likely represents survival bias. This is supported by the data, which demonstrate that a higher proportion of the patients who experience recurrent episodes of AKI have AKI Stage 1 at the index episode, while a higher mortality is related to AKI Stages 2 and 3. The longer term censored data, in contrast, suggest that mortality for all repeated episodes is similar and significantly higher than for a single episode. Our

**Table 3. Adjusted and unadjusted ORs for risk factors in predicting recovery from an AKI episode**

| | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P |
| Total number of episodes | | | | |
| 1 | Reference | – | Reference | – |
| 2 | 0.75 (0.71–0.79) | 0.000 | 0.79 (0.74–0.83) | 0.000 |
| 3 | 0.57 (0.52–0.62) | 0.000 | 0.61 (0.56–0.67) | 0.000 |
| ≥4 | 0.54 (0.49–0.59) | 0.000 | 0.56 (0.50–0.61) | 0.000 |
| Gender | | | | |
| Female | Reference | – | – | – |
| Male | 0.75 (0.73–0.79) | 0.000 | – | – |
| Pre-existing CKD | | | | |
| No | Reference | – | – | – |
| Yes | 0.71 (0.68–0.75) | 0.000 | – | – |
| AKI stage of index episode | | | | |
| Stage 1 | Reference | – | – | – |
| Stage 2 | 0.71 (0.67–0.76) | 0.000 | – | – |
| Stage 3 | 0.41 (0.39–0.44) | 0.000 | – | – |
| AKI type of index episode | | | | |
| CA | Reference | – | – | – |
| HA | 2.11 (2.02–2.21) | 0.000 | – | – |
| Age at index episode, years | 1.00 (1.00–1.01) | 0.000 | – | – |

[a]Adjusted for sex, pre-existing CKD, AKI stage of index episode, AKI type of index episode and age at index episode.
CI, confidence interval.

data also suggest that each additional episode of renal injury makes recovery of renal function less likely. Regression analysis showed that the likelihood of recovery was lower for patients with recurrent episodes compared with patients with a single episode. It should be noted that baseline renal function is reset at each AKI episode not to compound recovery data from 'hangovers' related to any preceding episodes. The data also suggest that each repeated episode carries a worse outcome, in terms of mortality and deterioration in renal function. This is a significant observation, as non-recovery from AKI is an important factor determining long-term outcome and CKD progression [9, 16, 21].

A first step in preventing recurrent AKI is to identify patients at highest risk of having multiple AKI episodes. The concept of a 'drug holiday' and the cessation of potentially nephrotoxic medication during an AKI episode, and also for those at risk of developing AKI due to an inter-current illness, are widely advocated. Generally, beyond either the acute AKI episode or the acute illness placing a patient at risk, current practice is to restart these medications. If there is a cohort of patients in whom the likelihood of recurrence can be predicted, the benefit of restarting such medication needs to be balanced by the risk of AKI recurrence. Our data suggest those most likely to have repeated episodes are older patients, with pre-existing CKD and those with incomplete recovery of their renal function following an acute episode. Interestingly, the data also suggest that patients from socially deprived areas are at higher risk of recurrent episodes. Previously, we have demonstrated that social deprivation is associated with higher incidence and worse outcome following AKI [22]. This was related to a greater burden of CKD at an earlier age. Interestingly, the severity of AKI at presentation of the index case was not useful in predicting recurrent episodes, despite a significant proportion of patients having AKI Stage 2 or 3. This is consistent with the observations of Liu *et al.* in which the severity of AKI was not associated with recurrent AKI [7]. This may in part be driven by higher rates of death observed in this population [3].

Current evidence suggests post-discharge care may improve outcomes for patients discharged from hospital following medical emergencies [23, 24]. For example, following acute myocardial infarction, early follow-up with a cardiologist is associated with decreased mortality and improved compliance with secondary preventative measures [25, 26]. The follow-up of patients following an AKI episode remains undefined. Not all patients who experience an episode of AKI can or should be followed up in a specialist clinic, given the large number of patients this would entail and the fact that in the majority of cases AKI is not indicative of intrinsic renal disease. Harel *et al.* [27], however, suggest specialist follow-up following AKI does translate into better outcomes. Their study suggested that nephrologist follow-up improves all-cause mortality of severe AKI survivors, although the study focused only on patients who required dialysis during an inpatient AKI episode. Published data suggest that <10% of patients who experience an episode of dialysis-requiring AKI see a nephrologist within the first year [28]. Dialysis-requiring AKI, however, represents only a small minority of patients who experience an episode of AKI. An alternative approach to identify who might benefit from specialist follow-up may be to highlight those most likely to experience recurrent AKI episodes. This would optimize a patient's chance of avoiding repeated AKI episodes, which are associated with poor outcomes. We suggest that patients with pre-existing CKD who suffer AKI and those whose renal function fails to recover to its pre-AKI baseline would be two overlapping cohorts that may benefit from specialist nephrology referral and follow-up.

Although this study is to our knowledge the first national study using an e-alert-based system to characterize the

magnitude and impact of recurrent AKI, its findings need to be qualified by its limitations. Using an IT-based approach precludes inclusion of clinical information, such as patient comorbidity and linkage to primary care data sets, and lacks the cause of AKI, the need for RRT and cause of death. As a result, we were unable to examine the relationship between patient clinical characteristics and the rate of AKI recurrence. Previous data suggest that patient-related chronic conditions such as heart failure, liver disease and cancer all associate with a higher rate of recurrent AKI [7, 8]. Future studies able to access detailed clinical data would allow development of a formal risk prediction tool for recurrent AKI using a similar approach to what we have used for the RISK study to predict an index episode of AKI [29]. Similarly, the use of biochemistry data precludes the use of urine output-based definitions of AKI, although it should be noted that these data are not systematically available and are rarely accessible to large population-based studies. Finally, the diagnosis of AKI is made by comparing creatinine values on an individual patient against previous results. This approach does consequently exclude patients with no previous measurements of creatinine on the system. An alternative suggestion has been the use of population-based estimated reference creatinine measures [30]. Currently, however, in our clinical setting when a creatinine value is above the reference range and does not generate an alert, a message to highlight the raised value accompanies the result report.

The strengths of our study include the size of the patient data set and the length of follow-up. To our knowledge, this is the largest published report addressing recurrent AKI with >150 000 AKI episodes. Due to its size, the data set included a substantial representation of all stages of AKI including those with more severe AKI, as well as a broad demography. The data therefore allow the results to be generalized to broader populations than previously published studies. Use of the e-alerting system provides access to cases of AKI that occur in both hospital and community settings, including primary care, and therefore overcomes some limitations inherent in studies of AKI in hospitalized cohorts or in which AKI diagnosis is reliant on hospital coding [31–34].

In conclusion, the results of this study provide an important contribution to the debate regarding the need for risk stratification for recurrent AKI. The data suggest that such a tool would be useful given the poor patient and renal outcomes associated with recurrent episodes of AKI as highlighted by this study. Further work is, however, required to determine the specific process of care and interventions to affect clinical outcomes in those patients at high risk of recurrent AKI.

## FUNDING

The work was carried out under the auspices of the Welsh AKI Steering Group, which is sponsored by the Welsh Renal Clinical Network and the Welsh Government.

## AUTHORS' CONTRIBUTIONS

J.H. analysed the data, produced the figures and wrote the report. J.D.W. and J.G. interpreted the data and wrote the report. A.O.P. set up the programme 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.

## CONFLICT OF INTEREST STATEMENT

None declared.

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**Appendix 4.1:** Published work 12 related to this thesis:

Holmes *et al*. (2016) 'Understanding Electronic AKI Alerts: Characterization by Definitional Rules', Kidney International Reports

KI REPORTS
KIReports.org
CLINICAL RESEARCH

# 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 μmol/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


Acute kidney injury (AKI) is a global health issue[1,2] characterized by an abrupt loss of kidney function that is strongly associated with high mortality and morbidity.[3–5] 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.

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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 $m^2$. 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,[5–7] 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[8] 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.

**Table 1.** E-alert rules: definition of rules that trigger the Laboratory Information Management System (LIMS) to send out the associated alert message to highlight the possibility of AKI to the requesting clinician

| Rule | Description | Associated alert |
|---|---|---|
| 1 | >26 μmol/l increase in creatinine in previous 48 h | Acute kidney injury (AKI) alert: rising creatinine within last 48 h |
| 2 | ≥50% increase in creatinine in previous 7 d | AKI alert: rising creatinine within last 7 d |
| 3 | ≥50% increase in creatinine against median result for previous 8–365 d | AKI alert—creatinine increase over the baseline value |

### 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.[9] 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 (CKDEpi eGFR) <60 ml/min per 1.73 $m^2$ 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*

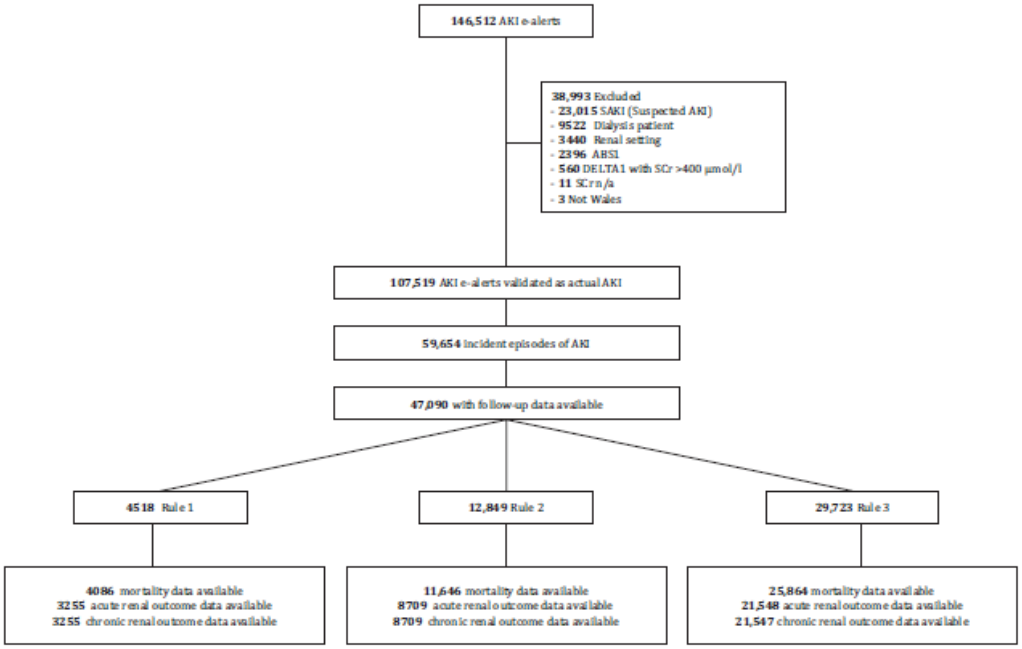


**Figure 1.** Cohort creation and exclusion criteria. SAKI (suspected AKI) is an e-alert generated by a >26 μmol/l increase in serum creatinine from a value recorded within the last 3–7 days and is not AKI by definition. ABS1 coded e-alerts and DELTA1 coded e-alerts generated by serum creatinine values >400 μmol/l have previously been validated as having high false positive rates.[8] AKI, acute kidney injury; SCr, serum creatinine.

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 ≥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

**Table 2.** Characteristics of the rule 1, rule 2, and rule 3 cohorts

| | Rule 1 | Rule 2 | Rule 3 |
|---|---|---|---|
| n (% of incident episodes) | 4518 (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 $m^2$) | 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 | 216.4 |
| Mean nadir eGFR associated with peak SCr (ml/min per 1.73 $m^2$) | 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) |
| Stage 3 | | 3.3 (421) | 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) | 18.4 (5463) |
| CA-AKI | 18.7 (844) | 17.7 (2267) | 66.0 (19,612) |
| 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 (798) | 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 138 cases (57, rule 1; 29, 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.

(rule 2, 32.4% vs. rule 1, 28.3% vs. rule 3, 26.6%, $P < 0.001$ for both comparisons), with no difference in mortality for rules 1 and 3 (Figure 2a). For AKI stage 1, mortality was significantly higher for rule 2 (30.1%) than rule 1 (27.4%, $P < 0.001$), which was significantly higher than rule 3 (23.3%, $P < 0.001$). For rules 2 and 3, mortality was significantly higher with each increase in AKI stage (Figure 2b). Mortality for each AKI rule was also associated with the time for repeated measurement of renal function that likely reflects the severity of the underlying clinical condition (median time to repeat measurement of renal function in those who died vs. surviving; rule 1: 1.00 ± 3.2 days vs. 1.02 ± 10.0 days, rule 2: 1.01 ± 3.9 days vs. 1.16 ± 10.1 days, rule 3: 1.02 ± 5.9 days vs. 1.78 ± 15.3 days, all $P < 0.001$).

The relationship between incident AKI episodes and subsequent renal function is shown in Figure 2c. Nonrecovery of renal function was lowest for rule 1 (7.9%) and significantly higher in both the rule 2 (22.4%, $P < 0.001$) and rule 3 (16.5%, $P < 0.001$) cohorts. Nonrecovery of renal function was more likely with increasing AKI stage, and for each AKI stage, nonrecovery was higher in the rule 2 than rule 3 cohort (Figure 2d).

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.[10] Given the lack of specific therapy, other than supportive measures, for established AKI, early intervention offers the best opportunity to improve patient outcomes.[11] Any improvement in clinical outcome will therefore be dependent on early detection to trigger prompt re-assessment of patients, close monitoring of patient

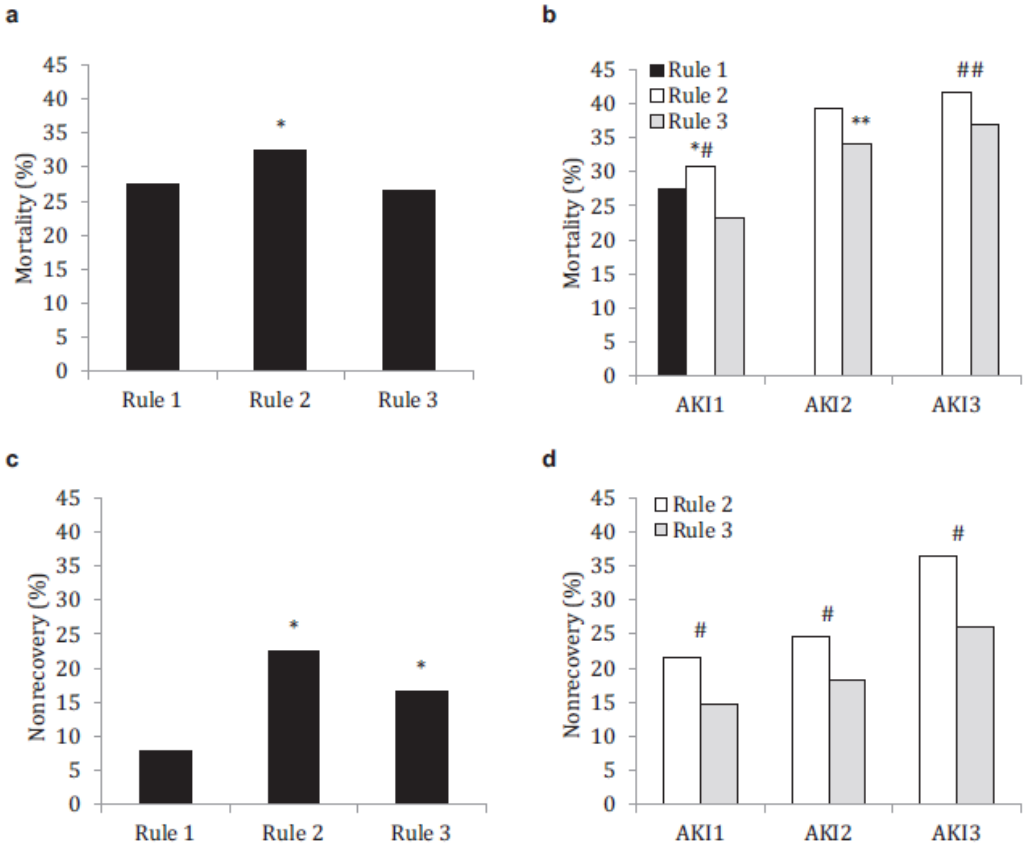


**Figure 2.** Differing outcomes associated with incident acute kidney injury (AKI) electronic alerts for AKI rules. (a) Ninety-day mortality rates, dividing according to the AKI rule. Mortality data were available for 41,596 patients (4086, rule 1; 11,646, rule 2; 25,864, rule 3). *$P < 0.001$ rule 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.

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.[12] 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.[13] The use of historical baseline values may therefore not be widely accepted by clinicians. Using strict definitions

**Table 3.** Characteristic comparison of those episodes generated by creatinine values within the population reference range with those generated by creatinine values outside the population reference interval

| | Within RR | Outside RR |
|---|---|---|
| n (% of incident episodes) | 9014 (19.2) | 38,072 (80.9) |
| Mean age ± SD (yr) | 63.8 ± 19.1 | 74.1 ± 14.7 |
| Sex, % (n) | | |
| Male | 42.6 (3838) | 48.5 (18,467) |
| female | 57.4 (5176) | 51.5 (19,605) |
| Pre-existing CKD, % (n) | 0.04 (4) | 43.8 (16,651) |
| Mean baseline SCr (μmol/l) | 50.5 | 99.9 |
| Mean baseline eGFR (ml/min per 1.73 $m^2$) | 104.3 | 65.0 |
| Mean alert SCr (μmol/l) | 81.8 | 189.9 |
| Mean peak SCr (μmol/l) | 101.5 | 224.2 |
| AKI severity, % (n) | | |
| Stage 1 | 95.4 (8598) | 73.2 (27,863) |
| Stage 2 | 4.3 (390) | 16.9 (6442) |
| Stage 3 | 0.3 (26) | 9.9 (3767) |
| Peak AKI stage, % (n) | | |
| Stage 1 | 72.9 (6574) | 54.8 (20,878) |
| Stage 2 | 16.1 (1452) | 24.7 (9420) |
| Stage 3 | 11.0 (988) | 20.4 (7774) |
| Clinical location, % (n) | | |
| HA-AKI | 50.8 (4578) | 38.7 (14,736) |
| CA-AKI | 41.0 (3696) | 50.0 (19,023) |
| Undetermined in hospital alerts | 8.2 (740) | 11.3 (4313) |
| Mean time to repeat ± SD (d) | 12.4 ± 31.8 | 6.0 ± 19.7 |
| Progression of AKI, % (n) | 23.4 (2103) | 25.4 (8714) |
| Stage 1 that progresses | 23.5 (2024) | 25.1 (6985) |
| Stage 1 that progresses to stage 3 | 10.3 (885) | 9.3 (2589) |
| Requirement of ICU, % (n) | 10.2 (916) | 10.1 (3830) |
| Repeat AKI episodes, % (n) | 19.1 (1192) | 19.1 (4500) |

Baseline eGFR data were missing for 135 cases (30 within RI; 105 outside RI) and excluded from the analysis of the pre-existing CKD variable.
AKI, acute kidney injury; CA-AKI, community-acquired AKI; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HA-AKI, hospital-acquired AKI; ICU, intensive care unit; RI, reference interval; RR, reference range; SCr, serum creatinine.

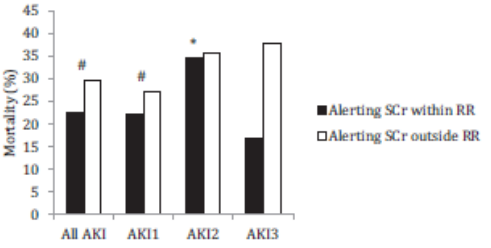


**Figure 3.** Mortality associated with incident acute kidney injury (AKI) electronic alerts for reference range classifications according to the AKI stage. Mortality data were available for 41,586 patients (32,446, stage 1 [7714, alerting SCr within RR; 24,732, alerting SCr within RR]; 5955, stage 2 [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.

that do not take into account preadmission biochemical results to generate AKI alerts are, however, likely to severely underestimate AKI incidence,[14] 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[15] and medication prescription.[16] Concerns have, however, been raised that the use of automated alerts may have unintended consequences related to overdiagnosis leading to overtreatment.[17] The generation of a large volume of alerts within the clinical environment drives a perception that the alert generates additional work that impedes workflow,[18] leading to "alert fatigue" causing clinicians to over-ride or disregard the alert.[19]

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[8] 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 rises in creatinine are associated with lower mortality in CKD.[20,21] Although the absolute increase in creatinine in this study was smallest for rule 1, it is of note that mortality for this group was not markedly reduced. Rule 2 was also associated with HA-AKI and had the highest mortality and nonrecovery. Rule 3 was the commonest cause of an alert and was associated with CA-AKI. Only a small minority of AKI is detected using the strict definition of a change in creatinine over the preceding 48 hours. Furthermore, a third of rule 1 based AKI represents AKI with normal baseline renal function, a group that carries a 90-day mortality over 20%. Mortality was highest in rule 2 alerting patients. Although there are no clear

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[22] with a significant proportion of these patients not being admitted to hospital.[8,23] CA-AKI represents a group of patients with more severe AKI (by AKI stage) at presentation than HA-AKI,[22] comparable 90-day mortality to HA-AKI for hospitalized patients,[8,22] and a significant impact on 3-year patient survival.[23] 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,[6,24–26] even when the increase in serum creatinine does not meet AKI criteria.[27]

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.

## ACKNOWLEDGMENTS

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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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**Appendix 4.2:** Published work 13 related to this thesis:

Holmes *et al*. (2017) 'The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert', Kidney International

# The incidence of pediatric acute kidney injury is increased when identified by a change in a creatinine-based electronic alert

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**A prospective national cohort study was undertaken to collect data on all cases of pediatric (under 18 yrs of age) acute kidney injury (AKI) identified by a biochemistry-based electronic alert using the Welsh National electronic AKI reporting system. Herein we describe the utility and limitation of using this modification of the KDIGO creatinine-based system data set to characterize pediatric AKI. Of 1,343 incident episodes over a 30-month period, 34.5% occurred in neonates of which 83.8% were AKI stage 1. Neonatal 30-day mortality was 4.1%, with 73.3% of this being accounted for by patients treated in an Intensive Care Unit. In the non-neonatal group, 76.1% were AKI stage 1. Hospital-acquired AKI accounted for 40.1% of episodes while community-acquired AKI represented 29.4% of cases within which 33.9% were admitted to hospital and 30.5% of cases were unclassified. Non-neonatal 30-day mortality was 1.2%, with half of this accounted for by patients treated in the Intensive Care Unit. Nonrecovery of renal function at 30 days occurred in 28% and was significantly higher in patients not admitted to hospital (45% vs. 20%). The reported incidence of AKI in children was far greater than previously reported in studies reliant on clinical identification of adult AKI or hospital coding data. Mortality was highest in neonates and driven by those in the Intensive Care Unit. Nonrecovery of renal function and persistent renal impairment was more common in non-neonates and was especially high in patients with community-acquired AKI who were not hospitalized.**

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KEYWORDS: acute kidney injury; electronic alert; pediatric nephrology



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Acute kidney injury (AKI) in children is associated with an extended hospital stay,[1] high inpatient mortality,[2] and a high incidence of long-term renal abnormalities.[3] In contrast to the high amount of data on adult AKI epidemiology, limited data are available regarding pediatric AKI, and few studies have reported regarding the population-based incidence and outcome of AKI in pediatric patients.[2,4]

On the basis of a presumption that the early identification of AKI helps increase the standard of care and improves patient outcomes, an automated real-time electronic-alert (e-alert) system for AKI using the Kidney Disease Improving Global Outcomes (KDIGO) criteria has been established and implemented nationally across the National Health Service in Wales. Alerts are transmitted as text attached to the report of creatinine findings. Creatinine values that generate alerts are also highlighted in red in the results reporting system to enhance their visibility to the requesting clinician. Using a centralized system of data collection, we previously reported the incidence and outcome of adult AKI, wherein the diagnosis of AKI was based on an e-alert system.[5] The current study used the national data set to describe the incidence and outcome of AKI in the pediatric population, when AKI is identified using an automated biochemistry-based electronic AKI alert system. Our aim was to determine the utility and limitation of using this creatinine-based AKI data set in pediatrics. In addition, the findings of 2 proposed interpretation methods that were based on the definition of AKI were compared with the findings of an approach that depends on the patient's previous laboratory results, as implemented in the e-alert algorithm.

## RESULTS

There were 2087 e-alerts (Table 1), representing 1343 incident AKI alerts, and the incidence rate was 1.37 cases per 1000 person-years for those under the age of 18 years. The overall 30- and 90-day mortality rates were 2.1% and 2.9%, respectively. Among all incident AKI alerts, 59.9% occurred in non-neonates and 40.1% in neonates.

### Non-neonate AKI

The mean age of AKI alert patients was 7.5 ± 6.1 years, and AKI was more common in boys (52%) than in girls (48%).

**Table 1 | Characteristics of the pediatric cohort**

| Variable | All pediatric patients | Neonates | Non-neonates |
|---|---|---|---|
| AKI e-alerts, n | 2087 | 837 | 1250 |
| Incident episodes (incident rate/1000) | 1343 (1.37) | 468 | 875 |
| Age, mean ± SD | 4.90 ± 6.04 yr | 4.5 ± 6.3 d | 7.5 ± 6.13 yr |
| Neonate, % (n) | 34.8 (468) | | |
| Male, % (n) | 54.6 (730) | 60.2 (278) | 51.7 (452) |
| bSCr (mg/dl), mean ± SD | 0.49 ± 0.61 | 0.43 ± 0.24 | 0.52 ± 0.73 |
| bSCr ($eCCl_{120}$) (mg/dl), mean ± SD | 0.32 ± 0.16 | 0.17 ± 0.00 | 0.40 ± 0.13 |
| bSCr (NormMid) (mg/dl), mean ± SD | 0.54 ± 0.22 | 0.38 ± 0.00 | 0.63 ± 0.23 |
| Preexisting CKD, % (n) | | | 6.1 (53) |
| Alert SCr (mg/dl), mean ± SD | 0.90 ± 1.30 | 0.73 ± 0.35 | 0.99 ± 1.58 |
| Peak SCr (mg/dl), mean ± SD | 0.99 ± 1.46 | 0.80 ± 0.43 | 1.09 ± 1.77 |
| AKI stage at alert, % (n) | | | |
| Stage 1 | 83.2 (1117) | 83.8 (392) | 82.9 (725) |
| Stage 2 | 11.6 (156) | 13.0 (61) | 10.9 (95) |
| Stage 3 | 5.2 (70) | 3.2 (15) | 6.3 (55) |
| Peak AKI stage, % (n) | | | |
| Stage 1 | 74.1 (995) | 70.3 (329) | 76.1 (666) |
| Stage 2 | 17.4 (234) | 22.0 (103) | 15.0 (131) |
| Stage 3 | 8.5 (114) | 7.7 (36) | 8.9 (78) |
| AKI rule, % (n) | | | |
| Rule 1 | 4.7 (63) | 8.8 (41) | 2.5 (22) |
| Rule 2 | 54.4 (731) | 88.9 (416) | 36.0 (315) |
| Rule 3 | 40.9 (549) | 2.4 (11) | 61.5 (538) |
| Progression of AKI, % (n) | 10.4 (140) | 14.7 (69) | 8.1 (71) |
| Time to peak SCr (d), mean ± SD | 6.31 ± 8.04 | 4.29 ± 6.27 | 8.20 ± 9.02 |
| HA-AKI, % (n) | | 91.0 (426) | 40.1 (351) |
| CA-AKI, % (n) | | 2.4 (11) | 29.4 (257) |
| Undetermined hospital alert, % (n) | | 6.6 (31) | 30.5 (267) |
| 30-day mortality, % (n) | 2.06 (25) | 4.14 (15) | 1.18 (10) |
| 90-day mortality, % (n) | 2.89 (35) | 5.52 (20) | 1.77 (15) |
| Nonrecovery at 30 days, % (n) | | | 28.2 (158) |
| Nonrecovery at 90 days, % (n) | | | 26.7 (168) |
| eGFR <50% of normal at 30 days, % (n) | 11.4 (107) | 6.9 (26) | 14.5 (81) |
| eGFR <50% of normal at 90 days, % (n) | 9.3 (92) | 4.2 (15) | 12.2 (77) |

AKI, acute kidney injury; bSCr, baseline serum creatinine; CA-AKI, community-acquired AKI; CKD, chronic kidney disease; e-alert, electronic alert; $eCCl_{120}$, estimated creatinine clearance; HA-AKI, hospital-acquired AKI; NormMid, normative midpoint.
Data on patient sex were missing for 7 cases (neonates, 6; non-neonates, 1), and these were excluded from analysis of the sex variable. Data on baseline eGFR were missing for 16 cases (neonates, 11; non-neonates, 5), and these were excluded from the analysis of the preexisting CKD variable. Mortality data were available for 1211 cases (neonates, 362; non-neonates, 849). Thirty-day SCr data were available for 939 cases (neonates, 378; non-neonates, 561). The mean time to the result used to determine the 30-day outcome was 15.4 ± 10.9 days (neonates, 18.3 ± 10.1 days; non-neonates, 13.4 ± 11.0 days), and the mean time to recovery was 4.3 ± 6.2 days (neonates, 4.3 ± 5.8 days; non-neonates, 4.2 ± 6.5 days). Thirty-day eGFR data were available for 936 cases (neonates, 376; non-neonates, 560). Ninety-day SCr data were available for 986 cases (neonates, 356; non-neonates, 630). The mean time to the result used to determine the 90-day outcome was 36.9 ± 30.9 days (neonates, 35.7 ± 29.5 days; non-neonates, 37.7 ± 31.6 days), and the mean time to recovery was 8.1 ± 15.1 days (neonates, 6.5 ± 11.9 days; non-neonates, 9.1 ± 16.8 days). Ninety-day eGFR data were available for 984 cases (neonates, 355; non-neonates, 629).

E-alerts classified the majority of cases as AKI stage 1 (76.1%), with 15% classified as AKI stage 2 and only 8.9% classified as AKI stage 3. Overall, 8.1% of patients showed renal function deterioration to a higher AKI stage. The largest number of alerts was generated by rule 3 followed by rule 2.

Hospital-acquired (HA) AKI accounted for 40.1% of all AKI episodes. Community-acquired (CA) AKI represented 29.4% of all incident episodes, and among these, 33.9% resulted in hospital admission within 7 days of the incident alert. For 30% of all alerts generated in an inpatient setting, the lack of information regarding the source of baseline serum creatinine (SCr) that triggered the alerts led to their classification as AKI from an undermined clinical setting (i.e., neither HA-AKI nor CA-AKI). Among all AKI patients, 12.6% were admitted to the intensive care unit (ICU) within 7 days of the incident alert.

***Comparisons to different baseline definitions.*** The definitional interpretation of AKI varies according to the choice of different baseline SCr values. For pediatric patients, particularly those with no historical biochemical data, the use of an estimated glomerular filtration rate (eGFR) of 120 ml/min per 1.73 $m^2$ to define "normal" baseline and the back-calculation of baseline SCr values or the use of normative values has been proposed.[6] We compared the findings of these 2 methods for obtaining baseline SCr values with the patient's actual baseline SCr identified using the national algorithm. The estimated baseline SCr value identified using the former method was significantly lower than that obtained from the patient's previous results (0.40 ± 0.13 mg/dl vs. 0.52 ± 0.73 mg/dl, $P < 0.001$). The average baseline SCr value identified using normative midpoint values more closely approximated the baseline SCr value from the patient's previous results (0.63 ± 0.23 mg/dl vs. 0.52 ± 0.73 mg/dl, $P < 0.001$). Bland-Altman analysis (Figure 1) demonstrated significant nonagreement between the algorithm and estimated baseline creatinine values regardless of the method used for baseline estimation, with progressively less agreement as estimated baseline values increased. Equal unit bias indicated an equal degree of agreement between the algorithm and estimated creatinine clearance criteria ($eCCl_{120}$) methods and between the algorithm and normative midpoint methods. The positive percentage bias confirmed that compared with the generation of a baseline using the algorithm (patient's actual baseline), the generation of a baseline using back-calculation from $eCCl_{120}$ is likely to underestimate SCr, leading to the over diagnosis of AKI.

***Outcomes.*** The 30- and 90-day mortality rates for the non-neonatal cohort were 1.2% and 1.8%, respectively, with patients treated in the ICU accounting for 50.0% of the 30-day mortality rate, and mortality was limited to only HA-AKI alerts. Linear regression analysis revealed that mortality was not associated with AKI severity (neither the AKI stage at presentation nor the peak AKI stage). The nonrecovery of renal function at 30 and 90 days was noted in 27.5% and 25.8% of patients, respectively. For patients who showed recovery of renal function following the alert, the mean time to recovery was 4.2 ± 6.6 days. The incidence of persistent renal impairment, as judged by eGFR of <50% of normal, was 14.3% at 30 days and 13.4% at 90 days.

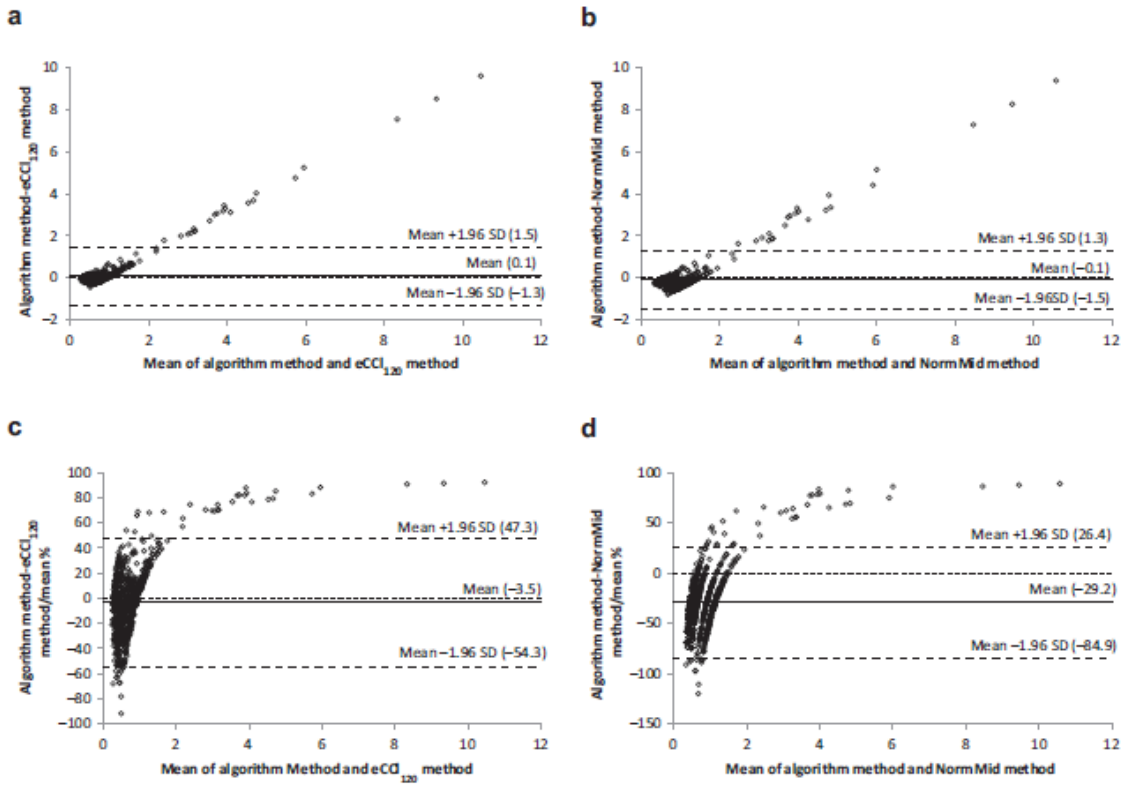


**Figure 1 | Comparison of the algorithm method with the estimated creatinine clearance criteria ($eCCl_{120}$) method and the midpoint normative (NormMid) method for baseline serum creatinine in non-neonates.** (**a**) Bland-Altman plot of the differences between the algorithm method and $eCCl_{120}$ method versus the mean of the 2 measurements, where differences are expressed as units (mg/dl). (**b**) Bland-Altman plot of the differences between the algorithm method and NormMid method versus the mean of the 2 measurements, where differences are expressed as units (mg/dl). (**c**) Bland-Altman plot of the differences between the algorithm method and $eCCl_{120}$ method versus the mean of the 2 measurements, where differences are expressed as percentage (%). (**d**) Bland-Altman plot of the differences between the algorithm method and NormMid method versus the mean of the 2 measurements, where differences are expressed as percentage (%). The bias is represented by the gap between the central dotted line, corresponding to zero differences, and the solid parallel line to the X-axis, which represents the mean. The dotted lines represent the lower and upper limits of agreement, from −1.96 SD to +1.96 SD.

Notably, the majority of alerts in the non-neonate group were derived from a baseline generated using the median creatinine for the preceding 365 days. This may be of concern, particularly in a pediatric cohort in which growth and changes in muscle mass influence creatinine values. However, in this cohort, the renal outcome for patients with an alert generated by rule 3 (≥50% creatinine increase from the median results within the last 8–365 days), as determined by the nonrecovery of renal function at 90 days, was comparable to the outcome for patients with an alert generated by rule 2 (≥50% creatinine increase within the previous 7 days), suggesting that alerts generated by both rules have similar clinical significance (nonrecovery: 26.1% rule 3 vs. 29% rule 2, $P = 0.43$).

The associations between admission to hospital and renal outcome for all CA-AKI alert groups are shown in Table 2. There was no difference in mortality between the hospitalized and non-hospitalized groups. In contrast, hospitalization was associated with a better outcome in terms of recovery from acute episodes at both 30 and 90 days and a lower proportion of patients with eGFR of <60 ml/min per 1.73 $m^2$ for the first time (this did not reach statistical significance at 90 days owing to the small number of patients). There was a positive association between the time to repeat assessment of renal function and hospitalization. The mean time to first repeat was significantly longer for patients who were not hospitalized than for those who were hospitalized (10.1 ± 8.8 vs. 1.1 ± 1.4 days, $P < 0.001$), suggesting that the absence of admission is associated with the lack of recognition of the significance of an AKI e-alert. Linear regression analysis revealed that a better acute outcome after adjustment was associated with hospitalization (hazard ratio 2.01, 95%

**Table 2 | Comparison of hospitalized and non-hospitalized pediatric patients with community-acquired AKI**

| Variable | Hospitalized | Non-hospitalized | *P* value |
|---|---|---|---|
| Number of episodes | 91 | 177 | |
| Time to repeat (d), mean ± SD | 1.1 ± 1.4 | 10.1 ± 8.8 | <0.001 |
| Progression of AKI, % (n) | 11.0 (10) | 2.8 (5) | 0.006 |
| Time to peak SCr (d), mean ± SD | 5.9 ± 8.0 | 19.7 ± 7.4 | <0.001 |
| 30-day mortality, % (n) | 1.1 (1) | 0.6 (1) | n/s |
| Nonrecovery at 30 days, % (n) | 20.0 (18) | 45.1 (23) | 0.002 |
| eGFR <50% of normal at 30 days, % (n) | 12.2 (11) | 25.5 (13) | 0.04 |
| 90-day mortality, % (n) | 1.1 (1) | 0.6 (1) | n/s |
| Nonrecovery at 90 days, % (n) | 16.4 (9) | 54.5 (18) | <0.001 |
| eGFR <50% of normal at 90 days, % (n) | 9.1 (5) | 21.2 (7) | n/s |

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; n/s, not significant; SCr, serum creatinine.
Mortality data were available for 254 cases (hospitalized, 90; non-hospitalized, 164). Thirty-day SCr and eGFR data were available for 141 cases (hospitalized, 90; non-hospitalized, 51). Ninety-day SCr and eGFR data were available for 88 cases (hospitalized, 55; non-hospitalized, 33).

confidence interval 1.29–3.23, $P = 0.003$) but was not associated with AKI severity, as measured according to either the AKI stage at presentation or the peak AKI stage.

### Neonates

E-alerts classified the majority of episodes as AKI stage 1 (83.8%), with 13% classified as AKI stage 2 and only 3.2% classified as AKI stage 3. Overall, 14.7% of the patients showed renal function deterioration to a higher AKI stage (Table 3). The majority of AKI cases (88.9%) were diagnosed using a baseline patient-derived SCr value generated within 7 days of the acute event (rule 2).

***Comparisons with different baseline definitions.*** The estimated baseline SCr value obtained with the method involving the use of eGFR of 120 ml/min per 1.73 $m^2$ as "normal" baseline and back-calculation of the baseline SCr value was significantly lower than that obtained from the patient's previous results (0.17 ± 0.00 mg/dl vs. 0.43 ± 0.24 mg/dl, $p < 0.001$), which can lead to over diagnosis of AKI. In contrast, the average baseline SCr value identified using normative midpoint values more closely approximated the baseline SCr value obtained from the patient's previous results (0.38 ± 0.00 mg/dl vs. 0.43 ± 0.24 mg/dl, $P < 0.001$). As in the non-neonate group, there was significant nonagreement between the baseline creatinine value according to the algorithm and estimated baseline creatinine values, regardless of the method used for baseline estimation, with progressively less agreement as the estimated baseline values increased. However, in this group, Bland-Altman analysis (Figure 2) and difference in unit bias demonstrated a stronger agreement between the algorithm and normative midpoint methods than between the algorithm and $eCCl_{120}$ methods.

Within the neonatal cohort, an additional concern has been raised regarding the possibility that errors in laboratory measurement among patients with very low SCr values will lead to over diagnosis of AKI. To overcome this, a modification of the KDIGO SCr-based criteria that involved a minimum SCr value of >0.5 mg/dl was previously applied[7] to identify AKI, on the basis of the normal SCr value in newborns on day 7.[8,9] Among all neonatal AKI cases flagged by an e-alert, 69.6% had a baseline creatinine value of <0.5 mg/dl. Of these cases, 52.4% showed an increase in the creatinine value to >0.5 mg/dl and 47.6% showed an increase in the creatinine value to ≤0.5 mg/dl. This latter group, which represented 33.1% of all neonatal AKI cases, could have been excluded if the aforementioned modification was applied.

**Table 3 | Characteristics of the neonate cohort with a baseline SCr value of <0.5 mg/dl**

| Variable | bSCr <0.5 mg/dl and increased to >0.5 mg/dl | bSCr <0.5 mg/dl and increased to ≤0.5 mg/dl |
|---|---|---|
| Incident episodes, n | 171 | 155 |
| Age (d), mean ± SD | 3.46 ± 0.01 | 8.96 ± 0.02 |
| Sex, % (n) | | |
| Male | 59.4 (101) | 62.6 (97) |
| Female | 40.6 (69) | 37.4 (58) |
| bSCr (mg/dl), mean ± SD | 0.38 ± 0.09 | 0.23 ± 0.04 |
| Alert SCr (mg/dl), mean ± SD | 0.70 ± 0.13 | 0.40 ± 0.06 |
| Peak SCr (mg/dl), mean ± SD | 0.78 ± 0.25 | 0.44 ± 0.12 |
| Progression of AKI, % (n) | 14.6 (25) | 13.5 (21) |
| Stage 1 progression | 17.5 (22) | 14.0 (18) |
| Stage 1 progression to stage 3 | 6.3 (8) | 1.6 (2) |
| Stage 2 progression | 9.4 (3) | 11.5 (3) |
| Time to peak SCr (d), mean ± SD | 4.16 ± 5.95 | 6.27 ± 8.18 |
| 30-day mortality, % (n) | 4.41 (6) | 0 |
| 90-day mortality, % (n) | 5.15 (15) | 0.78 (1) |
| eGFR <50% of normal at 30 days, % (n) | 5.3 (8) | 0 |
| eGFR <50% of normal at 90 days, % (n) | 2.8 (4) | 0 |

AKI, acute kidney injury; bSCr, baseline serum creatinine; CA-AKI, community-acquired AKI; CKD, chronic kidney disease; $eCCl_{120}$, estimated creatinine clearance; HA-AKI, hospital-acquired AKI; SCr, serum creatinine.
Data on patient sex were missing for 1 case, and these were excluded from the analysis of the sex variable for bSCr value of <0.5 mg/dl and increased to >0.5 mg/dl group. Mortality data were available for 264 cases (increased to >0.5 mg/dl, 136; increased to ≤0.5 mg/dl, 128). Thirty-day SCr and eGFR data were available for 253 cases (increased to >0.5 mg/dl, 151; increased to ≤0.5 mg/dl, 102). Ninety-day SCr and eGFR data were available for 241 cases (increased to >0.5 mg/dl, 141; increased to ≤0.5 mg/dl, 100).

***Outcomes.*** The 30- and 90-day mortality rates for the neonatal cohort were 4.1% and 5.5%, respectively. In the neonatal cohort, 46.6% of cases were treated in the ICU, and patients treated in the ICU accounted for 73.3% of the 30-day neonatal mortality rate. Additionally, 89.5% of patients (17 of 19 deaths) showed HA-AKI alerts. As in the non-neonate group, mortality was not associated with AKI severity (neither the AKI stage at presentation nor the peak AKI stage). In the entire neonatal cohort, the incidence of persistent renal impairment, as judged by eGFR of <50% of normal, was 4% at 30 days and 1.6% at 90 days. For patients with recovery of renal function following the alert, the mean time to recovery was 4.3 ± 5.8 days. As with the non-neonatal cohort, linear regression analysis revealed that renal outcome was not associated with the severity of renal injury, as

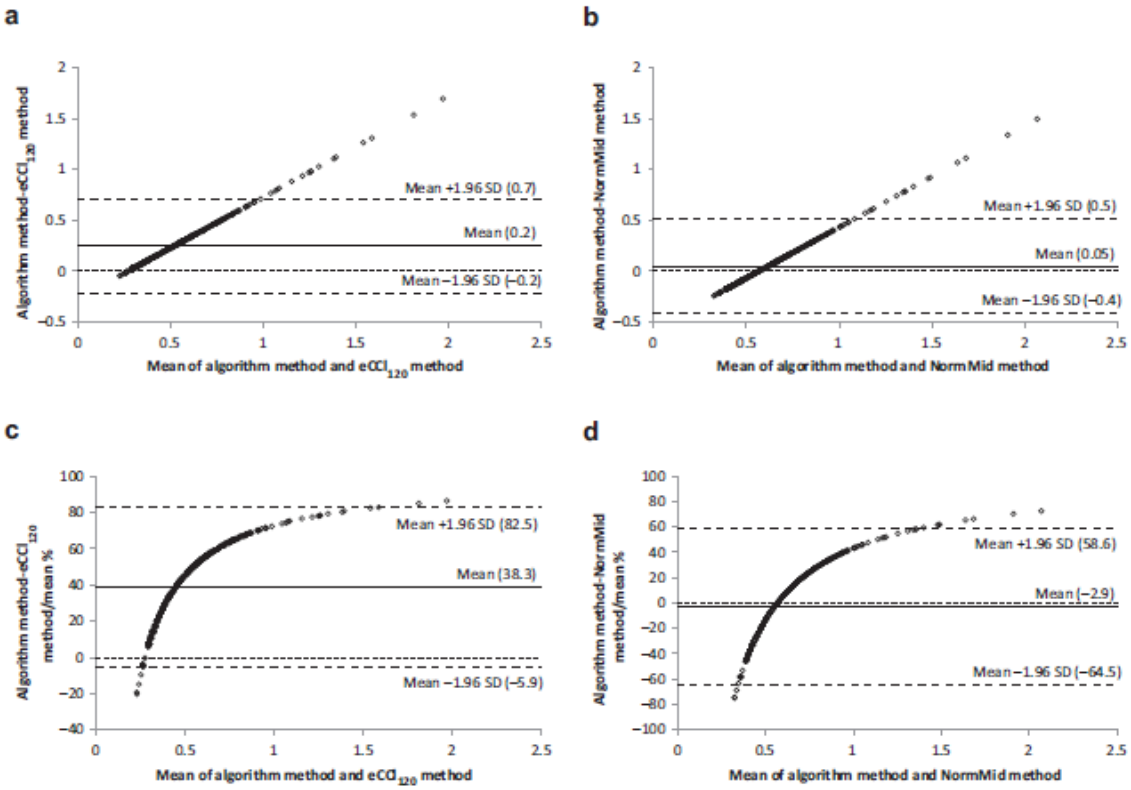


**Figure 2| Comparison of the algorithm method with the estimated creatinine clearance criteria ($eCCl_{120}$) method and the midpoint normative (NormMid) method for baseline serum creatinine in neonates.** (**a**) Bland-Altman plot of the differences between the algorithm method and $eCCl_{120}$ method versus the mean of the 2 measurements, where differences are expressed as units (mg/dl). (**b**) Bland-Altman plot of the differences between the algorithm method and NormMid method versus the mean of the 2 measurements, where differences are expressed as units (mg/dl). (**c**) Bland-Altman plot of the differences between the algorithm method and eCCl120 method versus the mean of the 2 measurements, where differences are expressed as percentage (%). (**d**) Bland-Altman plot of the differences between the algorithm method and NormMid method versus the mean of the 2 measurements, where differences are expressed as percentage (%). The bias is represented by the gap between the central dotted line, corresponding to zero differences, and the solid parallel line to the X-axis, which represents the mean. The dotted lines represent the lower and upper limits of agreement, from −1.96 SD to +1.96 SD.

measured using either the AKI stage at presentation or peak AKI stage.

Among patients who had an AKI e-alert with a baseline creatinine value <0.5 mg/dl and an increase to ≤0.5 mg/dl, there were no patient deaths, and no patient at 90 days had persistent renal impairment, as judged by eGFR of <50%. In contrast, among those who had an AKI e-alert with a baseline creatinine value of <0.5 mg/dl and an increase to >0.5 mg/dl, the mortality rates at 30 days (4.4%) and 90 days (5.2%) and the incidences of persistent renal impairment at both 30 days (3.6%) and 90 days (1.9%) were similar to the outcome measures for the entire neonatal group.

## DISCUSSION

The reported incidence of AKI varies depending on its definition, the clinical setting in which it is detected, and the population examined. Definitional differences make direct comparison of epidemiologic data challenging, potentially hindering the ability of the renal community to improve outcomes and highlighting the need to adopt a single and universal definition. This principle of a single diagnostic criterion underpins the adoption of a centralized laboratory-based definition of AKI in Wales. Many published studies[1–4,6,11] describing AKI focused on either HA-AKI or CA-AKI requiring hospitalization, and thus, failed to collect complete data regarding CA-AKI. In this study, in the non-neonatal group, CA-AKI represented almost one-third of all AKI cases, and of these, a significant proportion were not admitted to the hospital. Therefore, these cases were not incorporated into any analysis of CA-AKI based on admission to the hospital.

Our reported incidence is significantly higher than that previously reported in children. To date, 2 national data sets have been published describing the epidemiology of AKI in

children. A retrospective data set generated from the international classification of disease-10 codes in Norway reported an AKI incidence of 3.3 cases per 100,000 children among children aged under 16 years, suggesting an increasing incidence of AKI with time.[4] Possible explanations for the discrepancy in the incidence may be the presence of a true increase in the incidence since the termination of this study, the younger age cutoff for the definition of "pediatric," and the limitations associated with reliance on identification by coding. Sutherland *et al.* reported regarding the largest cohort of pediatric AKI cases to date and mentioned an AKI incidence of 3.9 cases per 1000 hospital admissions, although the reliance on the international classification of disease-9 coding likely led to the underestimation of AKI diagnosis.[2] In addition, data on AKI in the community were not collected. Both of these studies, as well as our data, demonstrated a male predominance. While a male predominance has been previously documented in the adult population with AKI,[2,4] such a finding has not been widely reported in the pediatric population. Both studies also demonstrated a bimodal age distribution with AKI in the very young group and the 15 to 18-year age group. Our data are consistent with these findings, and we demonstrated a high incidence of AKI in neonates.

The high incidence of AKI in the neonatal population in our study is likely partly attributed to our reliance on a creatinine-based definition. These young children had low SCr values, and therefore, small changes, even with the use of age-adjusted normal ranges, could trigger an AKI alert. One suggestion is the requirement of an increase in SCr values to >0.5 mg/dl for patients with a baseline SCr value of <0.5 mg/dl to generate an AKI alert to prevent over diagnosis of AKI in the neonatal cohort on the basis of the inherent error of laboratory measurements. Our data demonstrated that one-third of neonates, who fulfilled the requirement of the diagnosis of AKI according to the change in SCr values, belonged to the category with an increase in SCr values of <0.5 mg/dl. The lack of an association with either mortality or residual renal impairment supports the suppression of the alert for this specific group. This represents a pragmatic approach to avoid alert fatigue by reducing the rate of false positivity of the alerting system, although a change in creatinine within this range may represent a true episode of AKI in some cases, emphasizing the need for clinical scrutiny rather than total reliance on the alerting system designed to highlight the most "at-risk" patient groups. The relevance of an e-alert system in this cohort is limited by the lack of information, such as gestational age and the relevance of small changes in creatinine in low-birth-weight/premature infants, further supporting the suppression of alerts in the context of a "low creatinine" baseline. Creatinine-based definitions of AKI in neonates are also complicated by unique factors such as the presence of maternal creatinine, varying degrees of creatinine reabsorption in the proximal tubules, and maturation differences, particularly in sick neonates with persistent pulmonary hypertension and/or hypoxic ischemic encephalopathy.[10]

Mortality in our pediatric population was predominantly observed in neonates in the ICU and was consistent with the findings of previous publications. In the non-neonatal group, although mortality was much lower, it was largely observed in those patients admitted to the ICU. This is consistent with the recently published AWAreness during REsuscitation study in which AKI with regard to the ICU was associated with poor outcomes, including increased mortality.[11] Previous data in children suggested that outside the ICU group, there is no association between AKI and mortality, which likely reflects the nature of a pediatric population in which death is infrequent.[2,12] Notably, our reported mortality rate associated with AKI was significantly less than that reported in previous studies, which mentioned rates as high as 15%.[2] This may be explained by our definitional diagnosis that was based on biochemical parameters rather than on coding data, resulting in higher AKI capture rates. In addition, our data demonstrated that mortality was not associated with the degree of renal injury, at least when assessed by the change in SCr. Therefore, mortality is more likely to reflect the severity of the underlying disease that leads to impaired renal function.

Although mortality following AKI was significantly lower in the non-neonatal group than in the neonatal group, the converse was true for the development of persistent renal impairment. In the non-neonatal group, renal function did not return to normal in a significant proportion of patients, and approximately 15% developed eGFR of <50% of the age-adjusted normal value at 90 days. These data are particularly important because it is being increasingly recognized that this lack of recovery may translate into a long-term ongoing progressive renal injury.[3] At least in adults, recent data suggested that the 90-day SCr value is a legitimate surrogate end point for end-stage renal disease after AKI.[13]

A challenge for clinicians reporting AKI involves the ascertainment of baseline renal function. This is particularly important in pediatric patients for whom previous blood test results are often unavailable and is particularly challenging in neonates. It is clear that the variations in the AKI definition cause significant heterogeneity in terms of AKI diagnosis and reporting. Zappitelli *et al.* recently reported differences in the incidence from 4.6% to 43.1% in non-critically ill hospitalized children.[6] The accurate identification of AKI is an important goal because AKI, when associated with relatively small increases in SCr, is associated with adverse clinical outcomes in children.[14] As the e-alert system is based on a direct comparison of the current SCr value with the patient's own previous results, we compared this system with 2 previously suggested models to provide an estimate of baseline renal function in the absence of historic comparison. The argument for back-calculation based on eGFR of 120 ml/min per 1.73 $m^2$ has been previously reported.[6,15] However, our results clearly demonstrate that compared with the approach involving the patients' previous

results, this approach would lead to significant over reporting of AKI in children. In contrast, the use of the normative midpoint value provides a more accurate reflection of the true baseline value, and thus, may be the preferable approach for generating baseline estimations of renal function in the absence of previous measurements of renal function.

To our knowledge, this is the first national study using an e-alert–based system to characterize the magnitude and impact of AKI in children; however, its findings need to be qualified by its limitations. Our data reports the incidence of AKI, with a diagnosis according to a creatinine-based definition, wherein the baseline creatinine value may be generated on the basis of a blood sample obtained in the preceding 365 days. As such, this does not meet the strictly agreed AKI definition of "abrupt deterioration" and does not consider a urine output-based AKI diagnosis. Therefore, the discrepancies in the incidence between our data and previously reported data may partly be definitional. The number of blood tests performed is much lower in children than in adults, with recent data suggesting that <20% of inpatients will undergo repeated estimations of SCr during an inpatient admission.[16] Therefore, our definition addresses the lack of creatinine monitoring in noncritically ill young people. Another limitation is that any patient who presented with AKI but had no measurement of renal function in the previous 365 days was not included in our analysis, possibly resulting in underestimation of the true incidence of AKI. However, this approach does preclude the inclusion of the first presentation of AKI in a patient with no previous blood test results in the system. These patients are highlighted as patients with high creatinine. Detailed information regarding these patients is not included in this data set, and further investigations are needed. Using an information technology–based approach also precludes the inclusion of clinical information, such as patient comorbidity, patient volume status, and details of the cause of AKI. Despite these limitations, our study used a creatinine-based electronic AKI alert system to provide the first large scale description of the incidence and outcome of pediatric AKI. In addition, it provided a measure against which alternative models for predicting baseline renal function in children can be compared.

## METHODS

### Setting

Data on patients aged less than 18 years were collected from the laboratory information management system (LIMS) in Wales. These patients had an AKI e-alert. The study was approved under the terms of Service Evaluation Project Registration.

### Development of the electronic reporting system

The previously described and validated Welsh electronic AKI reporting system[5] utilizes an algorithm based on the changes in the SCr value and does not consider urine output (Supplementary Figure S1). Creatinine is measured using a kinetic Jaffe methodology on various analytical platforms across Wales. All methods are standardized using isotope dilution mass spectrometry–calibrated reference material. The LIMS (InterSystems TrakCare Lab, Cambridge, MA) generates an electronic AKI alert by automatically comparing measured creatinine values of an individual patient with previous results in the system. Therefore, an alert is only generated for patients who have previous results recorded. For patients with an increased creatinine value (above the laboratory reference value), no AKI alert is generated, although the abnormal result is highlighted to the requesting clinician with the following text "*Raised creatinine: if not known CKD suggest repeat to rule out Acute Kidney Injury.*"

Three rules are applied to generate alerts differing in the period at which the baseline creatinine value is obtained (Table 1). Rule 2 alerts represent a ≥50% increase in SCr values within the previous 7 days, rule 3 alerts represent a ≥50% increase in SCr values from the median of results from the previous 8 to 365 days, and rule 1 alerts represent a >26 μmol/l increase in SCr values within the previous 48 hours and is issued only if rules 2 and 3 are not satisfied. Repeat alerts are suppressed if the creatinine value identified is not greater than the previous values by 2CV% in the between-batch variation method, where CV is the coefficient of variation (SD expressed as a percentage of the mean). At present, the all Wales agreement is that 2CV is 6%.

### Data collection

Prospective data were collected for all cases of pediatric (<18 years of age) AKI from November 1, 2013 to April 30, 2016. Details of cohort creation are shown in Figure 3. All alerts occurring within 30 days of the first episode were defined as the same episode of AKI.

The incidence rate was calculated using Office for National Statistics (Newport, Wales, UK) population estimates from the middle of 2015.[17] If the first alert was issued during hospital admission after performing a blood test, which indicated a normal SCr value, in a hospital setting within the preceding 7 days, the patient was considered to have HA-AKI. If the alert was issued in a non-inpatient setting, the patient was considered to have CA-AKI.

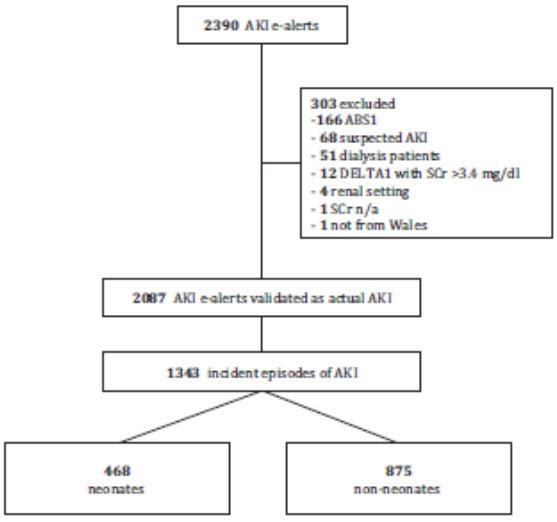


**Figure 3| Cohort creation, with exclusion and inclusion criteria.** AKI, acute kidney injury; DELTA1, code representing a >0.3mg/dl increase in creatinine within the last 48 hours and no other rule triggered; SCr, serum creatinine.

If the alert was issued in an inpatient setting with no available results for the previous 7 days, the patient was classified as "undetermined hospital alerts," as it was not possible to confidently consider the patient as having either CA-AKI or HA-AKI. Hospitalization of patients with CA-AKI was defined as the measurement of renal function in a hospital setting within 7 days of the alert. Patients were considered to have AKI treated in the ICU if AKI was alerted in the ICU or measurement of renal function was performed in the ICU within 7 days of the AKI e-alert. Progression of AKI was defined as a peak AKI stage higher than the incident e-alert, and for stage 3 alerts, progression was defined as ≥50% increase in the SCr value that generated the alert.

Mortality data were collected from the Welsh Demographic Service.[18] Patients were censored at 27 months for survival analysis. Renal outcome analyses performed at 30 and 90 days required patients to have follow-up data available and included only patients who survived at these time points.

Recovery was defined as an SCr value measured at or nearest to 30 days following the alert not consistent with the definition of AKI when compared with the baseline SCr value.

Persistent renal impairment was defined as eGFR of <50% of the age-adjusted normal value based on the SCr value measured at or nearest to 30 and 90 days following the alert. We calculated eGFR using the Schwartz method[9,19] and used age-related 50$^{th}$ percentile heights.[20] Preexisting CKD was defined as a baseline eGFR of <50% of normal.

Alternative definitions of baseline SCr[6] were derived using either $eCCl_{120}$ by assuming eCCl = 120 ml/min per 1.73 $m^2$ to back-calculate a baseline SCr or midpoint normative creatinine values for age and sex[21] as these are currently the reference ranges (Supplementary Table S1) used in Wales (Wales LIMS Harmonisation). These values were then compared with the national algorithm-derived baseline creatinine value.

### Statistical analysis

All statistical analyses were performed using the SPSS software, version 20 (SPSS, Inc., Chicago, IL). Student's *t*-test was used to analyze normally distributed data. Categorical data were compared using the Pearson chi-square test. A $P$ value less than 0.05 was considered to be statistically significant.

### DISCLOSURES

All the authors declared no competing interests.

### ACKNOWLEDGMENTS

JH and KM designed the study. JH and JG collected and analyzed the data. GR designed the study and validated the algorithm. JDW and KT interpreted the data and drafted the manuscript. AOP setup the program of work, designed the study, interpreted the data, and drafted the manuscript.

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.

### SUPPLEMENTARY MATERIALS

**Figure S1.** Algorithm for generating electronic alerts for acute kidney injury on the basis of serum creatinine (SCr) changes with time. Reference value (RV) defined as the SCr value with which the index SCr value is compared; D, difference between the current result and lowest previous result within 48 hours; RI, population reference interval.

**Table S1.** Normative serum creatinine values for age and sex. Source: Wales Laboratory Information Management System Harmonisation Group

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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**Appendix 4.3:** Screenshots of prototype tool developed by the author for QI in healthcare provision related to AKI

**Welcome to the national [PROTOYPE] NHS Wales AKI performance monitoring tool**

***Use the buttons below to navigate the tool.***

| Page | Description |
|---|---|
| Control charts | Use this page to monitor AKI performance in Wales over time, including at individual NHS Wales organisations and hospitals. |
| Funnel plots | Use this page to compare AKI performance in Wales over selected time periods, including performance between different NHS Wales organisations and hospitals. |
| Pareto charts | Use this page to investigate outlying AKI performance in Wales over time, including at individual NHS Wales organisations and hospitals. |
| Glossary | Use this page to better understand and interpret the data generated by, and terms used in, the tool. |
| Description of methods | Use this page to better understand the analysis and statistical process control techniques applied in the tool. |

***For any queries please contact [INSERT EMAIL HERE]***

Homepage | Control charts | Funnel plots | Pareto charts | Glossary | Description of methods

**Control charts** Homepage

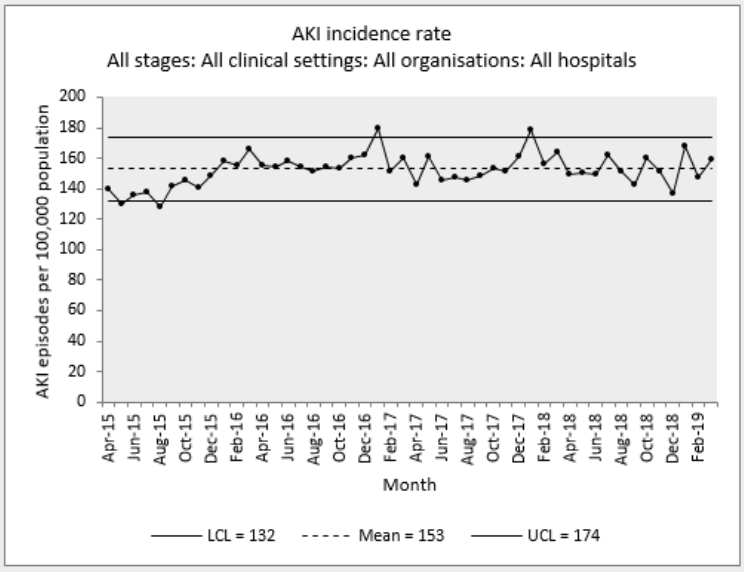
**Select indicator:** AKI incidence rate (per 100,000 population)

**Select severity of AKI:** All stages

**Select clinical setting of AKI:** All clinical settings

**Select NHS Wales organisation:** All organisations

**Select NHS Wales hospital:** All hospitals




Homepage | Control charts | Funnel plots | Pareto charts | Glossary | Description of methods

**Pareto charts** Homepage

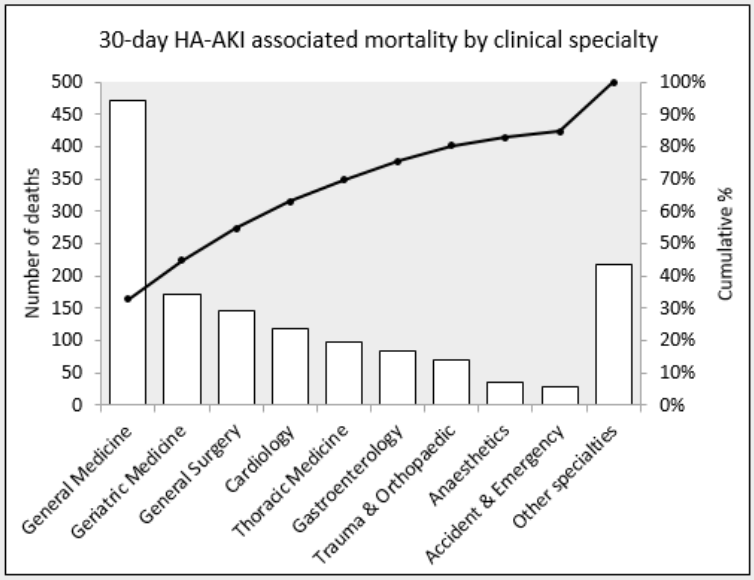
**Select indicator:** 30-day AKI associated mortality rate (%)

**Select severity of AKI:** All stages

**Select clinical setting of AKI:** HA-AKI

**Select NHS Wales organisation:** All organisations

**Select NHS Wales hospital:** All hospitals




Homepage | Control charts | Funnel plots | **Pareto charts** | Glossary | Description of methods

**Funnel plots** Homepage

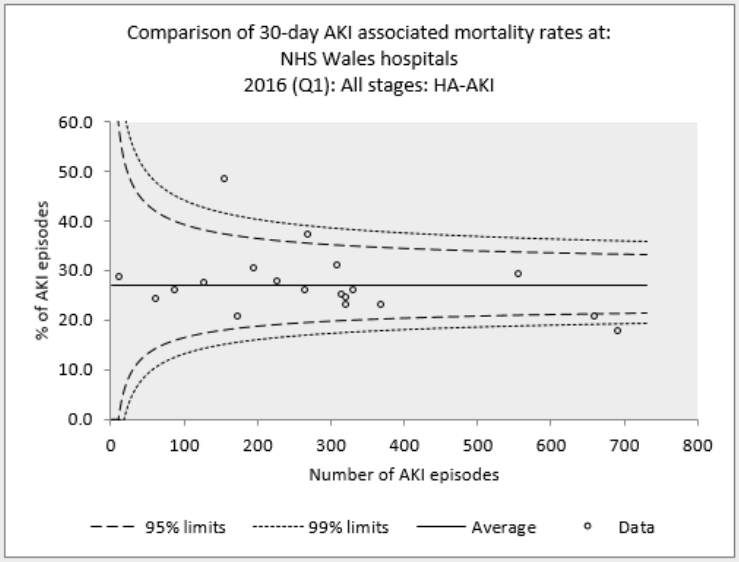
**Select indicator:** 30-day AKI associated mortality rate (%)

**Select parameter to be compared:** NHS Wales hospitals

**Select time period:** 2016 (Q1)

**Select severity of AKI:** All stages

**Select clinical setting of AKI:** HA-AKI




| Hospital | Num. of AKI episodes | Rate (%) | Lower 95% limit | Upper 95% limit |
|---|---|---|---|---|
| Hospital 1 | 14 | 28.6 | 0.0 | 73.6 |
| Hospital 2 | 62 | 24.2 | 4.9 | 45.5 |
| Hospital 3 | 89 | 25.8 | 8.6 | 42.4 |
| Hospital 4 | 128 | 27.3 | 11.6 | 41.0 |
| Hospital 5 | 156 | 48.1 | 13.1 | 40.2 |
| Hospital 6 | 175 | 20.6 | 13.9 | 39.5 |
| Hospital 7 | 196 | 30.1 | 14.6 | 38.6 |
| Hospital 8 | 228 | 27.6 | 15.5 | 37.7 |
| Hospital 9 | 267 | 25.8 | 16.4 | 36.7 |
| Hospital 10 | 271 | 36.9 | 16.5 | 35.6 |
| Hospital 11 | 310 | 31.0 | 17.1 | 35.0 |
| Hospital 12 | 317 | 24.9 | 17.3 | 34.7 |
| Hospital 13 | 322 | 24.2 | 17.3 | 34.7 |
| Hospital 14 | 323 | 22.9 | 17.3 | 34.7 |
| Hospital 15 | 332 | 25.9 | 17.5 | 34.4 |
| Hospital 16 | 369 | 22.8 | 18.0 | 34.1 |
| Hospital 17 | 557 | 29.1 | 19.7 | 33.8 |
| Hospital 18 | 662 | 20.4 | 20.5 | 33.7 |
| Hospital 19 | 693 | 17.5 | 20.6 | 33.7 |

Homepage | Control charts | **Funnel plots** | Pareto charts | Glossary | Description of methods

*Hospitals anonymised for confidentiality purposes.*

**Appendix 4.4:** Published work 14 related to this thesis:

Holmes *et al*. (2021) ‘Acute kidney injury demographics and outcomes: changes following introduction of electronic acute kidney injury alerts - an analysis of a national dataset’, Nephrology Dialysis Transplantation

Nephrol Dial Transplant (2020) 1–7
doi: 10.1093/ndt/gfaa071

ndt
Nephrology Dialysis Transplantation

ORIGINAL ARTICLE

# Acute kidney injury demographics and outcomes: changes following introduction of electronic acute kidney injury alerts—an analysis of a national dataset

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## ABSTRACT

**Background.** Electronic alerts for acute kidney injury (AKI) have been widely advocated. Our aim was to describe the changes in AKI demographics and outcomes following implementation of a National electronic AKI alert programme.

**Methods.** A prospective national cohort study was undertaken to collect data on all cases of AKI in adult patients (≥18 years of age) between 1 April 2015 and 31 March 2019.

**Results.** Over the period of data collection, there were 193 838 AKI episodes in a total of 132 599 patients. The lowest incidence of AKI was seen in the first year after implementation of electronic alerts. A 30-day mortality was highest in Year 1 and significantly lower in all subsequent years. A direct comparison of mortality in Years 1 and 4 demonstrated a significantly increased relative risk of death in Year 1: RR = 1.08 [95% confidence interval (CI) 1.054–1.114 $P < 0.001$]. This translates into a number needed to treat in Year 4 for one additional patient to survive of 69.5 (95% CI 51.7–106.2) when directly comparing the outcomes across the 2 years. The increase in the number of cases and improved outcomes was more pronounced in community-acquired AKI, and was associated with a significant increase in patient hospitalization.

**Conclusions.** This study represents the first large-scale dataset to clearly demonstrate that a National AKI alerting system which highlights AKI is associated with a change in both AKI demographics and patient outcomes.

**Keywords:** AKI, epidemiology, outcomes, prognosis, survival analysis

## INTRODUCTION

Acute kidney injury (AKI) is a common complication of multiple medical and surgical conditions, which carries significant morbidity and mortality and high health-associated costs [1]. The premise, that early and appropriate clinical intervention can improve the outcome for AKI [2], has driven the implementation of automated electronic AKI alerts across the National Health Service (NHS) in England and Wales. Implementation of electronic AKI alerts across Wales was established in April 2015. The system generates an alert based on real-time comparison of a serum creatinine with the patients' previous results with AKI defined by the KDIGO change in creatinine diagnostic criteria [3]. Using this system of electronic AKI alerts developed a centralized system of data collection to establish a National dataset encompassing all AKI alerts. Our previous data used this to characterize the epidemiology of AKI in both adults [4–9] and children [10]. The majority of previously published data focused on AKI in a hospital environment, but we have also characterized in some detail the nature of community-acquired (CA)-AKI [11, 12]. While the feasibility of implementation of AKI alerts is well documented in both hospital and community settings [13, 14], to date, it is unknown whether AKI alerts alter the patterns of AKI detection or impact patient outcomes [15].

Using our National dataset, and what is the largest cohort of AKI cases reported to date, we sought to examine the impact of the introduction of electronic AKI alerts by describing changes in AKI demographics and associated patient outcomes across all hospital and community healthcare settings in the first 4 years since the introduction of a national electronic AKI alert system in Wales.

## MATERIALS AND METHODS

Data from all Health boards in the NHS in Wales were collected from the Laboratory Information Management System on all patients aged ≥18 years between 1 April 2015 and 31 March 2019 that generated an AKI e-alert. The Medical Record Number, a unique reference number allocated to patients registered with the NHS in England, Wales and the Isle of Man, was

**Key learning points:**

What is already known. The use of AKI alerts is now common although little is known regarding their impact.
What this study adds. The data demonstrate a change in AKI demographic and outcomes following implementation of electronic AKI alerts.
What impact this may have on practice and policy. The data support the use of electronic AKI alerts to improve patient outcome.

used as the unique patient identifier. The programme of work has approval under the terms of Service Evaluation Project Registration.

The AKI alert is generated by comparing in real time a current creatinine value with historic creatinine values for the same patient. It defines AKI according to KDIGO increase in creatinine parameters [6]. The validation of the algorithm has previously been reported elsewhere [6, 16, 17]. We have previously demonstrated that this approach ensures the collection of all AKI episodes highlighted by an electronic alert across the country, regardless of the clinical location, and excludes patients with end-stage renal failure, receiving renal replacement therapy. The AKI alerts are displayed alongside the biochemical results on the pathology reporting system and consist of one of the following text statements, which provide context to the change in creatinine for the receiver:

(i) trigger ≥26μmol/L increase in creatinine within 48 h, associated alert; AKI alert: rising creatinine within the last 48 h;
(ii) trigger ≥50% increase in creatinine within 7 days; associated alert; AKI alert: rising creatinine within the last 7 days; and
(iii) trigger = 50% increase in serum creatinine against median result for 8–365 days; associated alert; AKI alert—creatinine increase over baseline value.

An incident AKI episode was defined as lasting 30 days, and the first AKI alert was defined as the incident alert, i.e. multiple alerts within 30 days of the incident alert were not considered new episodes. For patients with multiple episodes, the first episode was described as their index episode.

Episodes were classified as hospital-acquired (HA) AKI if the alert was issued in an inpatient setting and was accompanied by a normal creatinine value generated in an inpatient setting within the preceding 7 days. Episodes were classified as CA-AKI if the alert was issued in any non-inpatient setting, and this includes primary care and all non-inpatient settings in secondary care. Hospitalization of CA-AKI was defined as a measurement of renal function in an inpatient setting within 7 days following the alert. It was not possible to classify those AKI episodes which occurred in an inpatient setting but for which there were no results recorded in the previous 7 days as HA or CA. As such, these were classified as 'Undetermined in hospital alerts' and excluded from the subgroup analyses.

Data on patient mortality were collected from the Welsh Demographic Service, which electronically records the date of every registered death [18]. Progression of AKI was defined as a peak AKI stage higher than the alert AKI stage, or for Stage 3 alerts, a further increase in creatinine of ≥50% higher than the alert creatinine. Recovery of renal function was defined as the achievement of a creatinine value during the episode no longer in keeping with the definition of AKI when compared with the baseline creatinine value associated with the episode. Patients were only included in the progression and recovery analysis if they survived their episode and had at least one creatinine test during the episode. To identify pre-existing CKD, eGFR was calculated using the CKDEpi eGFR formula and defined as an eGFR <60 mL/min.

Statistical analysis was carried out using SPSS software, version 25 (IBM SPSS, Chicago, IL, USA). Student's *t*-test was used for the analysis of normally distributed data. Categorical data were compared using a Pearson Chi-squared test. The relationship between survival and AKI >4 years was analysed by Binomial logistic regression, with results presented both as unadjusted and adjusted for pre-existing CKD, AKI stage of index episode and age. Comparisons were made using Year 1 as the reference. $P < 0.05$ were considered statistically significant. 95% confidence intervals (CIs) for binomial data were defined as 1.96 multiplied by the standard error.

## RESULTS

All AKI episodes (Table 1): in the first 4 years since the introduction of the national electronic AKI alert system, there were a total of 193 838 AKI episodes in a total of 132 599 patients. HA-AKI represented 29.3% and CA-AKI 53.5% of all AKI episodes. The remainder (17.2%) represents undetermined in hospital alerts. Data on the population at risk during the 4 years were generated from data published by the Welsh Government Office of National Statistics [19] and is shown in Table 1. Over the 4 years, there was no statistical difference in the population number or age. Over the 4 years, the lowest incidence (and absolute number of episodes) of AKI was seen in the first year. The incidence of AKI was statistically greater in Year 2 (2023.4 versus 1854.6/100 00; $P = 0.006$) and Year 3 (1981.7 versus 1854.6/100 000; $P = 0.03$) when compared with Year 1. There was, however, no statistical difference in the incidence comparing Years 1 and 4. Comparison of the demographics of patients in Year 4 compared with Year 1 demonstrated a significantly

**Table 1. Comparison of patient demographics and outcomes for electronic AKI alerts**

| | All episodes | Year 1 | Year 2 | Year 3 | Year 4 |
|---|---|---|---|---|---|
| Number of episodes | 193 838 | 45 830 | 50 286 | 49 480 | 48 242 |
| Population at risk | | 2 471 198 | 2 485 244 | 2 496 876 | 2 508 846 |
| Median age of at-risk population | | 42.3 | 42.4 | 42.5 | 42.5 |
| AKI incidence rate (number of episodes per 100 000 population at risk) | | 1854.6 | 2023.4 | 1981.7 | 1922.9 |
| Number of patients | 132 599 | 37 242 | 40 657 | 40 340 | 39 371 |
| AKI incidence rate (number of patients per 100 000 population at risk) | | 1507.0 | **1635.9*** | **1615.6*** | 1569.3 |
| Patient age (mean ± SD), years | 70.37 ± 17.19 | 70.57 ± 17.13 | 70.53 ± 17.18 | 70.46 ± 17.12 | **69.93 ± 17.33†** |
| Male, % | 48.14 | 48.03 | 47.70 | 48.30 | 48.52 |
| Pre-existing CKD, % | 36.18 | 37.02 | 36.12 | 36.49 | **35.12†** |
| AKI, % | | | | | |
| Stage 1 | 75.1 | 74.9 | 74.9 | **76.1†** | **75.5*** |
| Stage 2 | 13.6 | 13.6 | 13.8 | 13.5 | 13.4 |
| Stage 3 | 11.3 | 11.4 | 11.3 | 11.6 | 11.1 |
| Repeat test in 30 days, % | 84.07 | 83.93 | 83.70 | 84.54 | 84.13 |
| Time to repeat test (mean ± SD), days | 3.4 ± 5.4 | 3.32 ± 5.35 | 3.45 ± 5.45 | 3.34 ± 5.37 | 3.40 ± 5.43 |
| Progression of AKI to higher stage, % | 10.19 | 10.45 | 9.98 | 10.30 | 10.07 |
| 30-day recovery of renal function, % | 82.71 | 83.23 | **82.58*** | **82.63*** | **82.42*** |
| Time to recovery of renal function (mean ± SD), days | 6.87 ± 7.99 | 6.89 ± 8.04 | 6.94 ± 8.01 | 6.85 ± 8.02 | 6.80 ± 7.93 |
| 30-day mortality, % | 17.84 | 18.59 | **17.6†** | **17.97*** | **17.15†** |

Recovery of renal function included only surviving patients with available tests of follow-up renal function: 133 092 episodes (31 144 episodes, Year 1; 34 647 episodes, Year 2; 34 447 episodes, Year 3; 32 854 episodes, Year 4) were included in the 30-day recovery of renal function analysis. Mortality data were available for 188 508 episodes (44 611, Year 1; 48 814, Year 2; 48 124, Year 3; 46 958, Year 4).

*$P < 0.05$ versus Year 1,

†$P < 0.001$ versus Year 1.

younger age of the patients at the time of the AKI episode, a significantly smaller proportion of patients with pre-existing CKD and a higher proportion of episodes presenting as AKI Stage 1.

The highest 30-day mortality was seen in the first year with significantly lower 30-day mortality in all subsequent years. A direct comparison of mortality in Years 1 and 4 demonstrated a significantly increased relative risk of death in Year 1: RR = 1.08 (95% CI 1.054–1.114; $P < 0.001$). This equated to a number needed to treat (NNT) in Year 4 for one additional patient to survive of 69.5 (95% CI 51.7–106.2) when directly comparing the outcomes across 2 years. Similarly, binary logistic regression demonstrated survival benefit for patients in all years compared with Year 1 (Year 2: OR = 1.11, 95% CI 1.07–1.14, $P < 0.001$; Year 3: OR = 1.04, 95% CI 1.01–1.07, $P = 0.029$; Year 4: OR = 1.06, 95% CI 1.03–1.10, $P = 0.001$). Following adjustment for age, pre-existing CKD and AKI stage at presentation, survival benefit remained significant when comparing Years 2 and 4 to Year 1 (Year 2: OR = 1.08, 95% CI 1.04–1.12, $P < 0.001$; Year 4: OR = 1.04, 95% CI 1.01–1.08, $P = 0.03$).

In contrast, while patient mortality improved over time, this was associated with a reduction in the recovery of renal function. This was significantly lower in all years compared with Year 1 (83.2% in Year 1 versus 82.3% in Year 2 versus 82.6% in Year 3 versus 82.4% in Year 4; $P < 0.05$). There was no difference across 4 years in the proportion of episodes, which progressed to a higher AKI stage. Similarly, the time to recovery of renal function was not different across the 4 years. We have previously used the proportion of patients with a repeat measurement of renal function within 30 days of the alert, and the time to said repeat measure of renal function as surrogate process measures. There were no changes in these parameters over the first 4 years of the national electronic AKI alert system being introduced.

HA-AKI (Table 2): subgroup analysis of HA-AKI episodes demonstrated no significant differences in patient demographics across 4 years. Progression of AKI was also not different over the 4 years. There was a significant improvement in patient mortality in Year 4 compared with Year 1 (23.9% versus 25.5%, $P < 0.05$). The relative risk of death in Year 1 compared with Year 4 was 1.06 (95% CI 1.02–1.11, $P = 0.003$) with an associated NNT of 64.7 (95% CI 58.8–193.8) in Year 4. Improved mortality outcome was again associated with a significant reduction in the proportion of patients who recovered their renal function in Year 4 compared with Year 1 (82.4% versus 83.2%, $P < 0.05$).

CA-AKI (Table 3): CA-AKI represented a significantly higher proportion of all AKI episodes in each of the Years 2–4 compared with Year 1. Similarly, the absolute number of episodes was also greater in each of the Years 2–4 compared with Year 1. Comparison of the demographics of CA-AKI patients in Year 4 with Year 1 demonstrated that patients in Year 4 were significantly younger (68.3 ± 17.9 versus 68.9 ± 17.7, $P < 0.001$), and a higher proportion of episodes presenting as AKI Stage 1 (70.8% versus 69.1%, $P < 0.05$). The proportion of AKI episodes associated with admission to hospital was significantly greater in Years 2–4 compared with Year 1 (21.2% in Year 1 versus 24.3% in Year 2 versus 24.4% in Year 3 versus 25.1% in Year 4). The 30-day mortality was significantly lower in Years 2 and 4 compared with Year 1 (14.4% in Year 1 versus 13.4% in Year 2 versus 13.2% in Year 4). A direct comparison of mortality in Years 1 and 4 demonstrated a significantly increased relative risk of death in Year 1: RR = 1.09 (95% CI

**Table 2. Comparison of patient demographics and outcomes for electronic HA-AKI alerts**

| | All episodes | Year 1 | Year 2 | Year 3 | Year 4 |
|---|---|---|---|---|---|
| Number of episodes | 56 857 | 13 955 | 14 642 | 14 415 | 13 845 |
| Number of patients | – | 12 700 | 13 311 | 13 121 | 12 623 |
| Patient age (mean ± SD), years | 72.50 ± 15.91 | 72.77 ± 15.85 | 72.73 ± 15.91 | **72.37 ± 15.92*** | **72.14 ± 15.98*** |
| Male, % | 49.94 | 49.92 | 48.98 | 50.58 | 50.32 |
| Pre-existing CKD, % | 31.44 | 31.44 | 31.70 | 31.37 | 31.23 |
| AKI, % | | | | | |
| Stage 1 | 84.7 | 85.1 | 84.2 | 87.9 | 84.8 |
| Stage 2 | 10.8 | 10.7 | 11.4 | 10.3 | 10.5 |
| Stage 3 | 4.5 | 4.2 | 4.4 | 4.8 | 4.7 |
| Repeat test in 30 days, % | 89.89 | 89.46 | 89.83 | 90.07 | 90.19 |
| Time to repeat test (mean ± SD), days | 1.91 ± 3.03 | 1.94 ± 3.11 | 1.92 + 3.02 | 1.87 ± 2.98 | 1.90 ± 3.01 |
| Progression of AKI to higher stage, % | 16.21 | 16.45 | 16.23 | 16.42 | 15.72 |
| 30-day recovery of renal function, % | 84.04 | 84.71 | 84.05 | 83.83 | **83.36*** |
| Time to recovery of renal function (mean ± SD), days | 5.98 ± 7.53 | 5.93 ± 7.39 | 5.94 ± 7.51 | 6.01 ± 7.66 | 6.02 ± 7.57 |
| 30-day mortality, % | 24.88 | 25.46 | 24.99 | 25.14 | **23.92*** |

Recovery of renal function included only surviving patients with available tests of follow-up renal function: 39 024 episodes (9489 episodes, Year 1; 10 067 episodes, Year 2; 9963 episodes, Year 3; 9505 episodes, Year 4) were included in the 30-day recovery of renal function analysis. Mortality data were available for 55 096 HA-AKI episodes (13 566, Year 1; 14 164, Year 2; 13 944, Year 3; 13 422, Year 4). *$P < 0.05$ versus Year 1.

**Table 3. Comparison of patient demographics and outcomes for electronic CA-AKI alerts**

| | All episodes | Year 1 | Year 2 | Year 3 | Year 4 |
|---|---|---|---|---|---|
| Number of episodes | 103 766 | 23 816 | 27 156 | 26 715 | 26 079 |
| Number of patients | – | 21 323 | 24 248 | 24 073 | 23 637 |
| Percentage of CA-AKI episodes (*n*) | 53.53 | 51.97 (23 816) | **54.00†** (27 156) | **54.00†** (26 715) | **54.06†** (26 079) |
| Patient age (mean ± SD), years | 68.89 ± 17.70 | 68.89 ± 17.67 | 68.98 ± 17.66 | 69.02 ± 17.63 | **68.27 ± 17.90*** |
| Male, % | 47.2 | 47.05 | 46.80 | 47.36 | 47.57 |
| Pre-existing CKD, % | 38.31 | 39.77 | 38.40 | 38.87 | 36.32 |
| AKI, % | | | | | |
| Stage 1 | 70.0 | 69.1 | **70.0*** | **70.0*** | **70.8†** |
| Stage 2 | 14.7 | 14.9 | **14.8** | **14.5** | **14.6** |
| Stage 3 | 15.3 | 16.0 | **15.2** | **15.5** | **16.6** |
| Admitted to hospital, % | 24.40 | 21.18 | **24.29*** | **24.93†** | **25.07†** |
| Repeat test in 30 days, % | 79.79 | 79.55 | 79.37 | 80.52 | 79.71 |
| Time to repeat test (mean ± SD), days | 4.63 ± 6.51 | 4.56 ± 6.49 | 4.71 ± 6.54 | 4.56 ± 6.46 | 4.68 ± 6.55 |
| Progression of AKI to higher stage, % | 7.37 | 7.48 | 7.19 | 7.53 | 7.28 |
| 30-day recovery of renal function, % | 80.88 | 81.33 | 80.57 | 81.01 | 80.67 |
| Time to recovery of renal function (mean ± SD), days | 7.85 ± 8.38 | 7.96 ± 8.56 | 7.98 ± 8.41 | **7.73 ± 8.32*** | **7.73 ± 8.25*** |
| 30-day mortality, % | 13.74 | 14.35 | **13.39*** | 14.05 | **13.22†** |

Recovery of renal function included only surviving patients with available tests of follow-up renal function: 704 784 episodes (16 003 episodes, Year 1; 18 557 episodes, Year 2; 18 473 episodes, Year 3; 17 445 episodes, Year 4) were included in the 30-day recovery of renal function analysis. Mortality data were available for 101 106 CA-AKI episodes (23 202, Year 1; 26 419, Year 2; 26 060, Year 3; 25 425, Year 4). *$P < 0.05$ versus Year 1. †$P < 0.001$ versus Year 1.

1.04–1.14, $P < 0.001$), which translates into an NNT in Year 4 of 88.27 (95% CI 57.3–192.3). Progression to a higher stage of AKI was not different over the 4 years. This was also the case for recovery of renal function; however, the time to recovery was statistically significantly shorter for Years 3 and 4 compared with Year 1 (8.0 ± 8.6 days in Year 1 versus 7.7 ± 8.3 days in Year 3 versus 7.7 ± 8.3 days in Year 4).

Our previous studies demonstrated that the majority of CA-AKI patients alert either at the time of presentation to hospital, in the Emergency Department, or as a result of a blood test taken in primary care [11, 12]. Table 4 compares the patient outcomes of these two cohorts over the first 4 years since the introduction of the national electronic AKI alert system in Wales. Analysis showed a significant reduction in 30-day mortality in Year 4 compared with Year 1 (20.9% versus 22.5% in the Emergency Department and 6.5% versus 7.6% in primary care, $P < 0.05$ for both). In the primary care cohort, improved mortality was associated with a significantly higher proportion of patients being admitted to hospital (17.1% in Year 4 versus 14.9% in Year 1, $P < 0.001$), and a higher proportion of patients with a repeat measurement of renal function within 30 days of the alert (72.5% in Year 4 versus 71.0% in Year 1, $P < 0.001$).

## DISCUSSION

Despite many improvements in clinical medicine, there is clear evidence that the incidence of AKI is increasing both in the UK [20, 21] and the USA [22, 23]. Currently, there are no specific

**Table 4. Comparison of patient outcomes for CA-AKI in primary care and the emergency department**

| | Year 1 | Year 2 | Year 3 | Year 4 |
|---|---|---|---|---|
| Emergency department | | | | |
| Number of episodes | 10 943 | 12 530 | 12 856 | 12 267 |
| Admitted, % | 38.00 | 39.22 | 38.33 | 38.78 |
| Repeat test in 30 days, % | 84.57 | 85.05 | 85.14 | 85.27 |
| Progression of AKI to higher stage, % | 7.87 | 7.35 | 7.32 | 7.75 |
| 30-day recovery of renal function, % | 89.07 | 89.10 | 89.58 | 88.87 |
| Time to recovery of renal function (mean ± SD), days | 4.98 ± 6.77 | 5.07 ± 6.83 | 4.99 ± 6.76 | 5.06 ± 6.89 |
| 30-day mortality, % | 22.47 | 21.62 | 22.14 | **20.90*** |
| Primary care | | | | |
| Number of episodes | 6525 | 7955 | 7596 | 7702 |
| Admitted, % | 14.91 | 15.78 | **17.14†** | **17.10†** |
| Repeat test in 30 days, % | 71.00 | 71.13 | **73.84†,‡** | **72.51*** |
| Progression of AKI to higher stage, % | 6.44 | 6.53 | 7.29 | 6.25 |
| 30-day recovery of renal function, % | 75.36 | 74.84 | 75.22 | 74.61 |
| Time to recovery of renal function (mean ± SD), days | 10.65 ± 8.07 | 10.29 ± 7.89 | 10.27 ± 8.04 | 10.12 ± 7.86 |
| 30-day mortality, % | 7.61 | **6.85*** | 6.94 | **6.53*** |

Recovery of renal function included only surviving patients with available tests of follow-up renal function. For Emergency Department AKI, 7348 episodes (Year 1), 8591 episodes (Year 2), 8820 episodes (Year 3) and 8277 episodes (Year 4) were included in the 30-day recovery of renal function analysis. For primary care AKI, 4123 episodes (Year 1), 5183 episodes (Year 2), 5125 episodes (Year 3) and 5014 episodes (Year 4) were included in the 30-day recovery of renal function analysis. Mortality data were available for 47 452 Emergency Department AKI episodes (10 678, Year 1; 12 199, Year 2; 12 568, Year 3; 12 007, Year 4) and 29 120 primary care AKI episodes (6376, Year 1; 7778, Year 2; 7419, Year 3; 7547, Year 4).

*$P < 0.05$ versus Year 1.

†$P < 0.001$ versus Year 1.

novel therapeutic interventions available for the treatment of AKI. This reflects the nature of AKI which is predominantly not caused by intrinsic renal disease. Deficiencies in the delivery of basic care in AKI are well reported. In the UK, the National Confidential Enquiry report in 2009 reported sub-optimal care in up to 50% of patients with AKI [24]. Given the lack of specific therapy for established AKI, other than supportive measures, the combination of prompt diagnosis, early clinical assessment of acute illness and volume status and urgent review of medications with appropriate temporary cessation of nephrotoxic ones still offers the best opportunity to improve patient outcomes [2]. Facilitation for early AKI detection and timely intervention is the rationale for introduction of electronic AKI alerts.

Despite this evidence to support the use of AKI alerts, there is neither little published data on the impact of alerts on detection of AKI, nor evidence to show that they change patient outcomes, even though their introduction is associated with improvement in care processes and earlier identification of AKI [14, 25–27]. A single-centre hospital-based randomized trial of e-alerts involving isolated use of a text message e-alert did not affect clinician behaviour or patient outcomes [28]. Similarly, the recent results of a randomized trial in the UK across five hospitals involving AKI alerts showed no benefit on patient mortality although this study did demonstrate reductions in hospital lengths of stay [29]. This lack of effect on patient-related outcomes has also been highlighted in a recent systematic review of currently available data [30]. In response to this, statements following the Acute Dialysis Quality Initiative consensus conference, which brought together experts in nephrology, critical care, epidemiology, informatics and biostatistics, highlighted the evidence care gap in the evaluation of electronic AKI alerts, and concluded that implementation should not be done without further evaluation of effectiveness [31, 32].

Our study represents the use of the largest AKI patient cohort reported to date to examine changes in AKI demographics and trends in outcome following implementation of a national AKI alert system. In addition, it provides data for the longest duration of time since the implementation of an electronic alert system. Our data suggest that the demographic of the patients in which AKI is being detected has changed over time. The introduction of AKI alerts led to an initial increase in AKI incidence, which was not apparent by the fourth year. This may represent an increased awareness of AKI leading to an increase in the number of blood tests requested although this is speculation as we do not have information on the absolute number of biochemistry requests. In addition, the data suggest that over the 4 years, AKI was detected in relatively a younger cohort with less pre-existing CKD detected in Year 4 compared with previous years. This may in part reflect more widespread 'AKI testing' related to an increased awareness of its significance in addition to the previously reported increased incidence of AKI [33]. The data also support the notion that electronic AKI alerts facilitate earlier detection as a higher proportion of patients presented with AKI Stage 1 in Years 2, 3 and 4 compared with the first year the alert system was in place. The data also demonstrate a temporal association of improvement in mortality over the 4 years since the introduction of the national electronic alert system. It is likely that this benefit reflects the larger patient sample compared with previous relatively smaller reported datasets. We also report that the improvement in mortality results in a trade off against a higher degree of residual renal impairment in the surviving cohort. While these factors are likely to influence patient-related outcome measures, even after correction for these, there was significant survival benefit in the years following introduction of AKI alerts.

This study also suggests that the largest impact of electronic AKI alerts can be found in CA-AKI and is most prominent in

primary care. Over the period of data collection, CA-AKI represents a higher proportion of all AKI episodes, suggesting more cases are being detected, and being detected at an earlier AKI stage. There is also a significant increase over time in the number and proportion of CA-AKI cases which are hospitalized. Our previous data on AKI in the community suggest that poor outcome is in part related to a lack of recognition and appropriate intervention, and that hospitalization while associated with the most severe AKI cases was associated with improved outcomes [11].

Data on the effect of electronic AKI alerts in the community setting are very sparse. Consistent with our data, a study confined to AKI Stages 2 and 3 with only 391 events, demonstrated improved response to AKI and reduced all-cause mortality [34]. The higher rates of hospital admission from the community is also consistent with a study which involved 9781 patients with AKI in primary care, and reported higher rates of creatinine monitoring and hospitalization from primary care following implementation of electronic reporting [35]. This study, however, did not report change in patient mortality, which in part is likely to reflect the relatively smaller number of AKI episodes in comparison to our data.

As the e-alert system is IT driven, it lacks 'intelligence' and therefore there is no clinical context applied. For this reason, the variation in serum creatinine seen in dialysis patients, unless specifically flagged by location, may lead to a number of false positives. We have previously reported our methodology to minimize the impact of inclusion of patients receiving renal replacement therapy [6]. Using these criteria results in a false-negative rate of 0.27% (exclusion of AKI patients) and a false-positive rate of 0.83% (inclusion of known dialysis patients). The study is also limited in that any patient presenting with AKI but without a measurement of renal function in the previous 365 days will not be included. Using an IT-based approach and a lack of linkage to primary care datasets also precludes inclusion of clinical information, such as the cause of AKI, renal replacement therapy or cause of death. Furthermore, the data are unable to shed light on the detail of any local AKI initiatives and clinical interventions, which may be responsible for the apparent improvement in outcome. While we acknowledge interventions and the models of their delivery might be varied, it can be assumed that all interventions to improve AKI outcomes involve simple clinical care solutions and are based on early assessment of the patient, adequate volume replacement, early treatment of sepsis and avoidance of nephrotoxic agents. During the period of data collection, there were no centralized/national care pathways or care bundles. Rather, the national launch of electronic alerts provided impetus for locally delivered quality improvement projects. The best mechanism for delivery of these clinical interventions is, however, beyond the scope of our dataset, but likely to be best tailored to local needs to improve awareness and develop care pathways. In addition, our data report the incidence of AKI in which the diagnosis is a creatinine-based definition in which the baseline creatinine may be generated based on blood samples taken in the preceding 365 days. As such, this does not meet the strict agreed AKI definition of 'abrupt deterioration', does not take into account a 'urine output'-based AKI diagnosis, and will not include patients with AKI but with no previous measurement of renal function for comparisons.

In conclusion, the study represents the first large-scale dataset to describe the change in AKI demographics associated with the introduction of a National AKI alerting system. The data also suggest that even accepting the changes in the AKI population, introduction of alerts is also associated with improved patient outcomes.

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## AUTHORS' CONTRIBUTIONS

J.H. designed the study, collected and analysed the data and produced the figures. J.D.W., K.D. and J.G. interpreted the data and wrote the report. AOP set up the programme of work, designed the study, interpreted the data and wrote the report.

## CONFLICT OF INTEREST STATEMENT

There are no competing interests.

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