Assessing the impact of acute kidney injury in secondary care and developing strategies to improve outcomes

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Lynne F Sykes

School of Medical Sciences,

Cardiovascular Division

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List of abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AKI	Acute kidney injury
ALD	Alcoholic liver disease
ANTT	Aseptic non-touch technique
App	Application
Appendix	Appendicitis
AQuA	Advancing Quality Association
ARB	Angiotensin II receptor blocker
BYOD	Bring your own device
CAP	Community acquired pneumonia
CB	Care bundle
Chole	Cholecystitis
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CMFT	Central Manchester Foundation Trust
COPD	Chronic obstructive pulmonary disease
COW	Computer on wheels
CQUIN	Commissioning for Quality and Innovation
CVA	Cerebrovascular accident
DECT	Digital enhanced cordless telecommunications
e-alert	Electronic alert
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ENT	Ears, nose and throat
EPR	Electronic patient record
g/dl	Grams per decilitre
g/l	Grams per litre
GIB	Gastrointestinal bleed
HF	Heart failure
HR	Hazards ratio

ICD-10	International classification of diseases (10^{th} edition)
ICU	Intensive care unit
IHI	International health institute
IM&T	Information management and technology
IT	Information technology
KDIGO	Kidney disease: Improving Global Outcomes
Mcmol	micromoles
Mmol	millimoles
N/A	Not available
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NICE	National institute for clinical excellence
POC	Point of care
NIHR CLAHRC	National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care
NOF	Neck of femur fracture
NTICB	Non traumatic intracranial bleed
OR	Odds ratio
Panc	Pancreatitis
PDSA	Plan Do Study Act
POC	Point of care
PPI	Patient and public involvement
QI	Quality improvement
RC	relative change
RRT	Renal replacement therapy
SCr	Serum creatinine
SKS	Salford kidney study
SPC	Statistical process control
SPSS	Statistical package for the social science
SQL	Structured query language
SRFT	Salford Royal Foundation Trust
TICB	Traumatic intracranial bleed
uPCR	Urine protein creatinine ratio

USCLIA	United States Clinical Laboratory Improvement Amendment
UTI	Urinary tract infection
WOW	Workstation on wheels

Abstract: Assessing the impact of acute kidney injury in secondary care and developing strategies to improve outcomes (**Dr Lynne Sykes)**
Introduction: Acute kidney injury (AKI) is associated with up to one in five emergency admissions to hospital and over 300,000 deaths per year in the UK. This thesis, presented in the alternative format, examines work undertaken to better describe the etiology of AKI in secondary care and then strategies to reduce AKI incidence, progression and complications.
Methods: Selected anonymised data from the hospital's 'data warehouse' was analysed using SPSS to calculate risk for mortality and critical care admission, analyse background user data, or calculate precision and bias of different point of care tests. The International Health Institute's Breakthrough Series Model was used for our quality improvement methodology.
Results: The literature review suggested education, an e-alert to trigger an AKI bundle and an in-built redundancy in the system were key to reducing mortality and critical care admission. The literature also demonstrates a high event rate of AKI and significant heterogeneity in cause and patient phenotype. The first three results chapters describe the epidemiology of our cohort of secondary care AKI patients in more detail. Chapters 3 and 4 examine the risks of different stages of AKI and the impacts they have on mortality, depending on admission diagnosis. Chapter 3 shows stark differences between patient mortality in those admitted with acute coronary syndrome and AKI 3 compared to those without AKI (OR 12.8 [4.8-33.8] $p<0.001$) and those admitted with fractured neck of femur and AKI 3 compared to those without (OR 24.6 [8.9-67.9]). In Chapter 4, the percentage of patients admitted with heart failure dying is similar in AKI 2 and AKI 3 (50% versus 47% respectively), demonstrating that escalating AKI stage does not always equate to escalating risk of mortality. Chapter 5 shows a specific 'at-risk' AKI population: patients with existing chronic kidney disease. Here, after a first AKI, subsequent episodes of AKI are more likely to be severe. Also, the risk for needing renal replacement therapy increases fourteenfold if a second AKI is stage 2 or 3, or twenty-eightfold if there are three or more episodes of AKI. The second three results chapters, Chapters 6, 7 and 8, describe the quality improvement work undertaken to reduce the incidence and progression of AKI, and also its complications. The large quality improvement programme is described in Chapter 6: it reduced hospital-acquired AKI by 22% and AKI progression by 48% on participating wards. The AKI collaborative group developed an AKI app to support education and signpost to references. Its use is detailed in Chapter 7. We compared results from point of care (POC) analysers with laboratory values in Chapter 8 and found that performance in the normal range showed excellent precision, and that in several scenarios POC tests could be used (with clinical judgment) to alter management.
Conclusion: This thesis uses big data to better describe the granularity of cases of AKI. Both the cause and effect of AKI can be heterogeneous and it should be seen as an 'illness barometer'. With early recognition, education and a set of actions within an AKI bundle, we have shown that AKI incidence and progression can be reduced.

Lay abstract

Acute kidney injury (AKI) is a rapid deterioration in kidney function. It is a common consequence of illnesses such as serious infections, and of serious states of dehydration. The kidneys are responsible for removal of waste products and also manage fluid and salt balance. If there are severe or acute changes in kidney function this can lead to a dangerous build-ups of waste products, fluid or salts.

Different conditions can place patients at greater risk of AKI — particularly older patients, those with serious heart or liver conditions, or those with existing kidney problems. This is owing to a combination of factors that can include changes in blood pressure (causing or as a consequence of these conditions) or the medications needed to manage the chronic condition.

AKI is associated with death and with long-term increased risk of heart attack or long-term poorer kidney function. This thesis looks at patients as they are admitted and their risk for death depending on the severity of the AKI they suffer, and how that is associated with the diagnosis they are admitted with.

Through improving our knowledge of these factors we then were able to start a programme of work using quality improvement methods to try to reduce the amount of patients who suffer AKI and reduce the progression to more severe stages if an AKI occurrs.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses.

Justification for journal format

This PhD thesis is presented in the alternative format. The Introduction and Results chapters take the form of manuscripts that have been published (Chapters 1, 3, 5 and 6) or are suitable for publication in a peer-reviewed journal (Chapters 4, 7 and 8). The exception is the generic methods chapter (Chapter 2) that provides general methods and population information with the specific methods for each results chapter or manuscript detailed in the specific results chapter.

The results chapters (Chapters 3 to 8) provide their own abstract, introduction and methods, preceded by an introductory rationale to explain the context within the thesis. For the introductory and results chapters that are published the heading corresponds to the title of the published or submitted article. As per submitted manuscripts, after the title there will be a list of co-authors and a link to the relevant journal publisher's Intellectual Property Rights policy, covering use of any published material in this thesis. Tables and figures for the manuscripts are embedded in the texts they are associated with. Each chapter has its own references at the end. This format is in accordance with the University of Manchester policy on presentation of theses.

The alternative thesis format was considered appropriate as each results chapter contains distinct sections of work that have been, or will be, submitted to peer-reviewed journals as standalone papers. As they address a common theme there may be some unavoidable repetition.

Dedication

Ad astra per aspera

I must acknowledge not just all those I've named here, but also those that surround me and support me. I am immensely grateful to my supervisors, family and friends, who have been my greatest cheerleaders.

This is for those who have inspired me, challenged me and helped me find my way.

And above all, to caffeine and sugar, without which, none of this would be possible.

This one is for you.

The Author

I completed medical school with an MbChB from the University of Sheffield in 2010. I then completed foundation and core medical training in the North East of England before starting my current post as a dual renal and general internal medicine registrar in the North West Deanery.

The opportunity to participate with clinically relevant and engaging research in acute kidney injury arose through an out-of-programme training post at Salford Royal Foundation Hospital. This post allowed me to enrol for a PhD with the University of Manchester, work as a quality improvement fellow and develop my interest in acute kidney injury through the quality improvement collaborative.

The success and calibre of this research allowed me to engage and network with the wider acute kidney injury community and brought opportunities to present work both nationally at UK Kidney Week and AKI Frontiers, and internationally at the European Renal Association (ERA) in Madrid and Budapest, at the American Society of Nephrology (ASN) in Chicago and the Society of Acute Medicine (SAM) in Amsterdam.

This thesis has led to opportunities not only within the topic of acute kidney injury but also in acute medicine. I have developed writing skills through submission of a chapter on acute kidney injury and chronic kidney disease for urology registrars.

Throughout the research for this PhD I have also maintained clinical acumen through gaining generic instructor training to teach on Advanced Life Support and the IMPACT (Ill Medical Patients Acute Care and Treatment) course. All of these clinical and research skills will enable me to continue research in acute kidney injury to improve processes of care and outcomes for patients.

Contribution of the author

The supervisors — Dr. Rob Nipah (RN) and Professor Philip A. Kalra (PAK) — conceived the idea of the clinical research post and applied for the business case, securing funding from the Emergency Assessment Unit at Salford Royal Foundation Hospital. Dr Lynne Sykes (LS) set out the hypothesis and design for each of the individual chapters, supported by PAK and Dr Darren Green (DG) for all chapters, RN for Chapters 1 and 6, and Dr James Ritchie (JR) for Chapters 5 and 7.

LS was solely responsible for liaison with the data analysis team and worked closely with Emma Flanagan (EF) to develop the code for data retrieval from the data warehouse. LS attended a coding course and statistical analysis course, both at the university and at the University of Nottingham to develop SPSS skills and R skills. The majority of analysis was using SPSS, supported by DG. The thesis was written entirely by LS with editorial support from her supervisory team and other colleagues as detailed below.

Chapter 1 was conceived, designed and written by LS, supported by RN, DG and PAK.
Chapter 2 was conceived, designed and written by LS with support from DG.
Chapter 3 was conceived, designed and written by LS (who also performed data analysis) with support from DG. The data collection was completed with support from EF and there was peer review from PAK.
Chapter 4 was conceived, designed, analysed and written by LS with support from DG. The data collection was completed with support from EF.
Chapter 5 was initiated by PAK with Ozgur Azar (OA), with data collection and curation by JR, Dr Dianna Vasallo, Dr Maharajan Raman and Dr Helen Alderson. The hypothesis, analysis and development of the chapter was by LS and DG, with statistical support from OA and Peter Diggle (PD). It was written by LS with support from DG and peer review from PAK.
Chapter 6 was developed with RN and the quality improvement team at Salford Royal Hospital with support from Dr Janet Hegarty, Dr Smeeta Sinha, Dr Dimitrios Poulikakos, Dr Paul Ferris, Elizabeth Lamerton and Emma Flanagan. RN was the AKI lead for the AKI collaborative. LS presented at the collaborative sessions,

supported the collaborative wards, provided clinical feedback on PDSA (plan, do, study, act) cycles and did off-site comparative work in Liverpool and Manchester with their quality improvement teams. LS lead the education work stream, delivered multidisciplinary team education, developed the online Moodle education resources and helped with data analysis and presentation. The chapter was conceived and written by LS, with support from RN and peer review from DG and the authors listed.

Chapter 7 was conceived, designed, and written by LS (who also performed data collection and analysis) supported by JR with peer review from DG.

Chapter 8 was conceived, designed and written by LS (who also performed data analysis) with support from DG. The data collection was with support from EF and peer review from PAK.

Chapter 9 was conceived, designed and written by LS with support from DG.

Chapter 1

A narrative review of the impact of interventions in Acute Kidney Injury

1.1 Rationale

In this introduction we explore the rationale and literature behind this PhD. The literature review details acute kidney injury (AKI) following the National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) Report in 2009: 'Adding Insult to Injury'. This report highlighted AKI as a common and serious syndrome that was under-recognised and poorly managed within the NHS in England. This literature review sought to identify aspects and elements of research from the wider community that made impactful differences to AKI incidence, dialysis incidence, critical care admission and mortality in patients with AKI.

This chapter has been published and is therefore included in this thesis in its original format however further developments are discussed in Chapter 9 'Discussion and Future Directions'.

It has been published in the Journal of Nephrology.

J Nephrol (2018) 31: 523. DOI: 10.1007/s40620-017-0454-2

1.2 Abstract

AKI is independently associated with significant morbidity and mortality, and is thus an important challenge facing physicians in modern healthcare. This narrative review assesses the impact of strategies employed to tackle AKI following the 2009 NCEPOD report on AKI.[1]

There is scarce and heterogeneous research into hard end points such as mortality and AKI progression for AKI interventions. This review found that e-alerts have varying effects on mortality and AKI progression, but decrease the incidence of contrast-induced AKI. The use of AKI bundles delivers statistically significant improvements in mortality and AKI progression. Similarly, AKI nurses generate statistically significant improvements on hospital acquired AKI and mortality. As yet there is no evidence base for the effects of education, sick day rules and smart phone apps.

Overall, a combination of e-alerts and AKI bundles supported by education yielded the most effective and statistically significant results. Current practice revolves around reactive rather than preventative behaviour. This narrative review discusses reactive interventions and their impact on the progression and severity of AKI, and on mortality from it. Preventative behaviour, such as risk stratification and early intervention in the deteriorating patient, may be influential in decreasing AKI incidence.

1.3 Introduction

1.3.1 Overview

AKI is an important challenge facing physicians in modern healthcare. AKI is a common and serious syndrome present both in the community and in hospital populations. It is characterised by an acute deterioration in renal function and classified into Stages 1, 2 and 3 as shown in Table 1-1.

Table 1-1. KDIGO Acute Kidney Injury classification

AKI	Serum creatinine criteria	Urine output criteria
Stage 1	Increase of more than 0.3 mg/dl (≥ 26.4 μmol/l) or increase of 1.5 to 2 fold from baseline	< 0.5 ml/kg per hour for 6-12 hours
Stage 2	Increase 2 to 3 fold from baseline	< 0.5 ml/kg per hour for >12hours
Stage 3	Increase 3-fold or serum creatinine of more than or equal to 4.0 mg/dl (> 354 μmol/l) or initiation of renal replacement therapy	Less than 0.3 ml/kg per hour or anuria for >12hours

A US single centre study of more than 15,000 emergency admissions to hospital found that AKI accounted for more than 1 in 5 of the presentations.[2] In a United Kingdom single centre study, 65% of AKIs identified had commenced in the community.[3] Specific sub-groups of patients are at particularly high risk of AKI, such as the elderly and those with pre-existing CKD. AKI is independently associated with significant morbidity and mortality, with a mortality of 23.9% in adults (95% CI, 22.1 to 25.7) shown in a 2013 meta-analysis.[4] AKI is linked with significant healthcare costs,[5] with 'the cost of ignoring AKI' priced at £1.2 billion in the UK.[6]

This narrative review focuses on patient outcome of interventions employed to tackle AKI through changes in both investigation and management. A narrative review has been conducted because the lack of high quality studies for each intervention, combined with the heterogeneity of both study design and population, makes it difficult to produce a reliable systematic review or meta-analysis. This review will focus on studies since the seminal NCEPOD report of 2009.[7]

1.3.2 NCEPOD report 2009: 'Adding insult to injury'

The NCEPOD report 'Adding Insult to Injury: A review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure)' in 2009 was chosen as a cut-off for review, as it was a milestone in the recognition of AKI, elevated its profile, and was a factor in the increase in studies of AKI interventions in the United Kingdom in recent years. This report stressed several key concerns in recognition and investigation of AKI, and highlighted poor adherence to basic clinical investigation protocols in a consistent and timely fashion. It

emphasised that less than 50% of care was deemed good, while 43% of patients with hospital-acquired AKI had an unacceptable delay in recognition. Overall, the panel felt that there was poor recognition of sepsis, acute illness, and hypovolaemia. They concluded that 17% of hospital-acquired AKI could have been avoided. Underlying this, they described a failure to complete basic investigations and continue baseline physiological monitoring.[7]

1.3.3 Interventions post-NCEPOD

Several interventions have been developed with the aim of achieving significant improvements in the care of patients in hospital to both prevent and detect AKI, and to focus on swift management after identification.

In response to the NCEPOD report, the Commissioning for Quality and Innovation (CQUIN) instigated financial rewards for improving AKI care. In 2015/16 NHS England supported CQUIN's financial rewards strategy by allowing NHS commissioners to offer such rewards to healthcare service providers under the NHS standard contract, providing the indicators detailed in Figure 1-1 were complied with. Previously, when the Advancing Quality Alliance (AQuA) pursued a similar strategy to focus attention on pneumonia, they found that a 6% reduction in mortality was achieved, as well as a saving of £10 for every £1 spent.[8]

Figure 1-1. CQUIN indicators 2015/2016 for Acute Kidney Injury

The percentage of patients with AKI treated in an acute hospital whose discharge summary includes each of four key items:

1. Stage of AKI (a key aspect of AKI diagnosis)

2. Evidence of medicines review having been undertaken (a key aspect of AKI treatment)

3. Type of blood tests required on discharge; for monitoring (a key aspect of post discharge care)

4. Frequency of blood tests required on discharge for monitoring (a key aspect of post discharge care).

1.3.4 Aims of this review

Several initiatives followed the NCEPOD report of 2009 and led to the development of the 2015 CQUIN targets. They reinforced several developments in the race to improve recognition of AKI and the ways in which healthcare professionals are alerted to investigate and initiate management. The aim of this review was to look at whether the specific interventions of electronic alerts (e-alerts), AKI nurses, AKI bundles, AKI apps for electronic devices, education, and sick day rules have improved outcomes for patients with AKI.

1.4 Review method

A preliminary scoping exercise was undertaken. It indicated that the studies available were too heterogeneous to permit a systematic review or meta-analysis of the interventions developed to tackle AKI. This was due to both heterogeneity of the AKI definition in the preceding years – RIFLE, AKIN and KDIGO criteria were all used, and additionally heterogeneity of the interventions and the wrap-around resources, in terms of AKI nurses, outreach teams, IM&T or research support and MDT education. Therefore a narrative review of the literature from January 2009 to

November 2016 was undertaken using computer and internet databases. The review focused on the period following 2009, since it was in that year that AKI started to attract significant media and medical attention and was pushed to the forefront of the national agenda following publication of the NCEPOD report.

The databases searched were NHS evidence, CINAHL, EMBASE, Medline and PubMed, Google Scholar and the Cochrane Library. There was an additional review of relevant references in the selected final papers. Studies were selected that considered adult patients only, had a defined intervention (AKI bundle, AKI nurse, e-alert, sick day rules, education package, AKI app), and a measured outcome (mortality, renal morbidity, change in creatinine, dialysis, AKI progression, AKI incidence). AKI progression was defined according to the KDIGO criteria and defined as an increase in numerical AKI stage or new requirement for renal replacement therapy.

The specific search keywords used are shown in Table 1-2, below. Each vertical column was combined using the Boolean operator OR. Each vertical column group was then combined using AND with the AKI column group.

Table 1-2. Key words used as Boolean operators or in search for articles.

AKI	E-alert	Specialist nurse	AKI bundle	AKI app	Sick day rules	Education
Acute kidney injury	Electronic alert	Nurse	Bundle	Applica-tion	Sick day	Education package
Acute renal failure	E alert	Outreach		App	Sick day cards	Teaching
Acute renal impair-ment	Electronic flag			Smart-phone	Sick day guidan ce	
ARF	Alert			Smart phone		

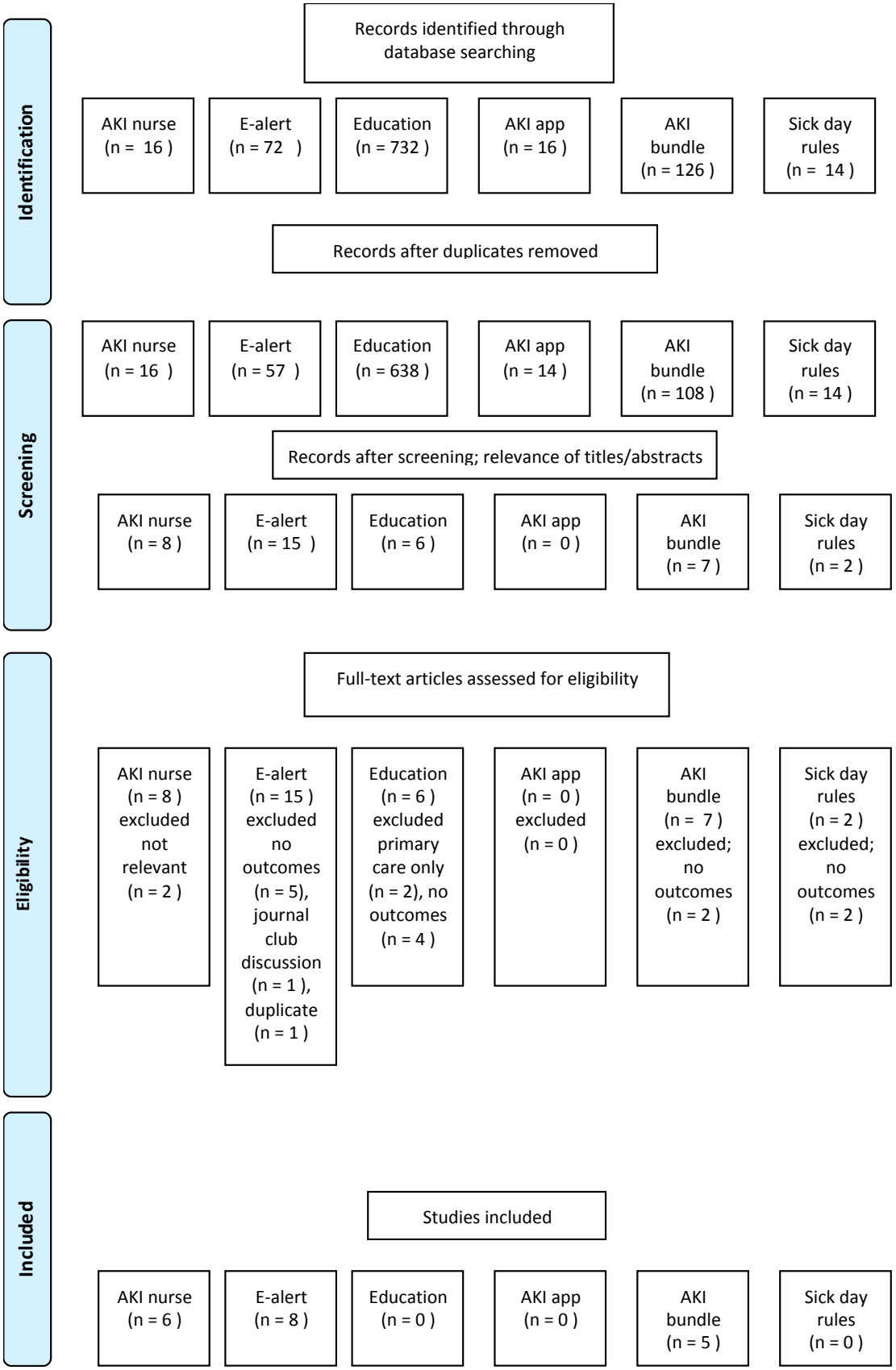
Papers were initially screened by title. At this stage duplicates and unrelated papers were excluded. After this initial refinement, the papers were then reviewed by abstract to determine relevance. All study designs were eligible. Finally, the full paper was reviewed and judged against the following inclusion criteria:

- Exclusively considered adults over the age of 18
- Rooted in secondary care, hospital only
- Written in English, from any country
- Published 2009-2016, in full and peer reviewed
- At least one AKI intervention (e-alert, specialist nurse, education package, AKI bundle, AKI app)
- At least one AKI outcome measured from the following - mortality, renal morbidity or change in creatinine or dialysis, AKI progression, AKI incidence

The total number of articles related to AKI and each intervention at each stage of the review process are found in Figure 1-2.

There has been ongoing literature review and discussion with regards to this chapter that appear in Chapter 9.

Figure 1-2. Number of articles meeting the criteria for inclusion by category



The criteria were decided upon prior to the review being undertaken to create a robust framework while reviewing articles, and to ensure this review aligned with future research work that is planned by the department.

The main reasons for exclusion were concerned with no measured outcome related to AKI progression, mortality or incidence. The majority of seemingly relevant studies were excluded during review of the paper as they focussed on compliance with the intervention, rather than the effect the intervention had on AKI. Another significant section of papers covered epidemiological aspects of AKI that were generated from the advent of the e-alert.

1.5 Results

The results discussed are those prior to 2018 when this was published, with further key papers discussed in Chapter 9.

1.5.1 E-alerts

The introduction of the mandatory e-alert system has standardised criteria for AKI staging with a national algorithm for detection. This was established by NHS England in March 2015 and rolled out over the following year across primary care.[5]

There have been numerous heterogeneous studies on the topic of e-alerts and their impact, generating a slowly growing body of evidence. As far back as 1994 Rind et al.[9] laid foundations for the current national algorithm with software that tracked creatinine, for over 1500 episodes of AKI, and sent an alert to the email of the responsible physician. This improved the average time from change in creatinine to change in nephrotoxic medication by 21.6 hours (p=0.0001) with a risk of serious renal impairment of 0.45 (95% CI 0.22 to 0.94) when compared to the control period.

Table 1-3 summarises the e-alert studies included in this review. A single centre study in Belgium by Colpaert et al found an increase in the number of early therapeutic interventions, (28.7% in e-alert group vs. 7.9% and 10.4% in the pre- and post e-alert control groups, respectively, $p < 0.001$). In the e-alert group, more patients received fluid therapy (23.0% vs. 4.9% and 9.2%, $p < 0$ .01), diuretics (4.2%

vs. 2.6% and 0.8%, p <0 .001), or vasopressors (3.9% vs. 1.1% and 0.8%, p <0.001). However there was no change in length of stay in ICU, mortality, or severity of AKI[10]. This highlights balancing factors: the negative impact that interventions can have such as an increased workload or increased interventions with no related clinical improvement.

Table 1-3. Studies showing the effect of e-alerts on outcomes in AKI

Study	Number of patients	Setting	Outcome	Comment
Mortality				
Colpaert (2012)[10]	951 patients (Pre-alert control group 227; Alert group 616; Post alert control group 236)	ICU	No effect on mortality; mortality p=0.37 Increase in early 28.7% in e-alert group vs. 7.9% and 10.4% in the pre- and post e-alert control groups, respectively, p =< 0.001	AKI with DECT phone alert, effect of AKI sniffer disappeared post intervention
Thomas (2015)[11]	157 pre intervention 251 post intervention	Hospital	No effect on mortality at 4 years	Intervention; e-alert. Initial 6% improvement in survival of post intervention group
Wilson (2015)[12]	1192 usual care 1201 intervention	Hospital	No effect on mortality; (Odds ratio 1·16 [0·81–1·68]; p=0·40).	Intervention; pager alert for AKI with link to website
Ebah (2017)[13]	Number not declared, Quality improvement project; interventional before and after study	Hospital	Trend towards lower mortality 34 per month, vs 38 per month prior to intervention	Care bundle, AKI nurse, education
Selby (2013)[14]	8411 post alert, CB, education	Hospital	Decreased mortality p=0.006	Unadjusted survival at 30 days improved from 76.3% to 80.5% over 6 months

Kolhe (2015)[15]	1209 pre alert 1221 post alert with CB	Hospital	Decreased in-hospital mortality p=0.046	Mortality benefit persisted at 30, 60 and median follow up of 134 days for those with CB completed within 24 hours of AKI
Chandra sekar[16]	Quality improvement project interventional study	Hospital	23.2% reduction in in-hospital mortality 25.9% reduction in 30-day mortality sustained over 33 months	Combined with care bundle, AKI nurse, education
AKI progression, creatinine rise or dialysis incidence				
Colpaert (2012)[10]	951 patients (Pre-alert control group 227; Alert group 616; Post alert control group 236)	ICU	No effect on AKI progression or dialysis incidence	AKI progression p=0.09, dialysis incidence 0.68 More and earlier interventions for AKI with DECT phone alert, effect of AKI sniffer disappeared post intervention
Wilson (2015)[12]	1192 usual care 1201 intervention	Hospital	No improvement in AKI progression (p=0.81) or the incidence of dialysis (Odds ratio 1·25 [95% CI 0·90–1·74]; p=0·18)	AKI progression p=0.81, dialysis incidence (OR 1·25 [95% CI 0·90–1·74]; p=0·18)
Kolhe (2015)[15]	1209 pre alert 1221 post alert with CB	Hospital	Less AKI progression p=0.01	
AKI Incidence				
Chandra sekar (2016)[16]	Quality improvement project interventional study	Hospital	Decrease in AKI 3	Combined with care bundle, AKI nurse, education
Ebah[13]	Number not declared, Quality improvement project; interventional before and after study	Hospital	31% reduction in incidence of AKI (9 to 6.5% admission incidence) hospital acquired (28% reduction)	Care bundle, AKI nurse, education

Cho (2012)[17]	258 pre 205 post alert	Hospital	Reduced incidence of Contrast induced-AKI p=0.02	More contrast prophylaxis, 55% post vs. 25% pre alert

OR=odds ratio; CB=care bundle; CI-AKI=contrast induced AKI.

Wilson et al. produced the largest study of e-alerts post NCEPOD. This single centre study from the USA screened 23,364 adult patients, randomly assigning 1,192 patients to standard care and 1,201 patients to the intervention arm. They found alerts to be ineffective at improving outcomes.[12] They described an alert system for the intervention arm that relied on paging an automated electronic alert to the responsible medical provider and pharmacist for each for AKI within 1 hour of the alert. This alert contained a hyperlink to a website of study information and the latest KDIGO AKI guidelines. There was a parallel control group who received standard care without an alert. Overall there was no change to the way AKIs were managed, the website was not visited more frequently and nephrology referrals were not significantly increased. There was no improvement seen in AKI progression (p=0.81), the incidence of dialysis (odds ratio 1·25 [95% CI 0·90–1·74]; p=0·18) or mortality between the groups (odds ratio 1·16 [0·81–1·68]; p=0·40). Most importantly, there was no improvement in survival. A smaller, UK-based single centre study by Thomas[11] that relied on the automated national e-alert detection system found similar conclusions, however this was not randomized like the previous study. There was a mean age of 70 and around 80% of those patients with alerts were admitted to hospital. The intervention involved the primary clinical care team receiving a phone call to advise them on AKI management. They detected an initial 6% improvement in survival with the intervention group. However, this was no longer statistically significant when followed up at 4 years (p=0.38 log rank test). Thomas' study differed from Wilson's by including a follow-up phone call to the team after the automated e-alert. This additional phone call or interaction appears to have an influence on human behaviours and may be what drives e-alert success.

How an e-alert is communicated is important to its acceptance – the process by which a fact is considered valid and adopted into clinical practice. As such, weaknesses in the format of an alert and/or the method of its delivery may account for failures to translate alerts into action. Technological and human elements combine in a complex relationship in an e-alert. Several of those elements typically

combine to affect an e-alert's efficacy, including placement, impact, frequency or intrusiveness of alerts within the software. Another issue is a high incidence of deferring or overriding alerts.[1819] Human factors such as habituation, banner blindness and alert fatigue are all key influences. Phansalkar et al. describe large pressures on the NHS from organisation, reorganisation and time shortage.[20]

E-alerts that were linked to an intervention have yielded positive outcomes in terms of AKI incidence, AKI progression and AKI mortality. A key example of a proactive, rather than reactive, intervention is by Cho et al. [17] in the context of adult in-patients in a single centre and contrast prophylaxis. Cho linked an interruptive e-alert for the physician to consider contrast prophylaxis at the time of CT request for all patients with an eGFR < 60ml/min/1.73m^2. This intervention led to a significant reduction in contrast induced AKI (CI-AKI) (p=0.02) with a significant increase in contrast prophylaxis prescription in the intervention group of 55% vs. 25%.[17] Selby published a cautiously optimistic observational assessment from service developments of 8411 patients from a single UK centre. He reported lower mortality with the combination of e-alert, care bundle and an education package. The unadjusted survival data at 30 days showed an improvement in survival from 76.3% to 80.5% over 6 months.[14]

A propensity score-matched cohort single centre study of 2297 patients by Kolhe et al. that used a care bundle to support the interruptive e-alert also found a significant decrease in mortality (p=0.046, OR 0.46-0.89) that persisted for up to 4 months in multivariable analysis. This had a hazards ratio of 0.77 for those patients with AKI bundles completed within 24 hours.[15] None of the subsequent studies have long enough follow-up periods or sufficient long-term data to prove sustained improvement in mortality. The notable difference between those studies that demonstrated positive outcomes appears to be the introduction of a care bundle or interruptive checklist alongside the e-alert. It is likely that this secondary element, alongside the inevitable rise in profile of the intervention with education and awareness, is creating a redundancy within the system that allows AKI to be more reliably identified and its treatment to be instigated earlier.

Ebah and Chandrasekar[13,16] each conducted quality improvement projects using a variety of tools to improve the recognition, investigation and management of AKI.

These two studies had similar interventions: AKI nurses, education, an AKI bundle and e-alerts. The significant differences were that Ebah's Manchester team developed an e-alert that was highly sensitive – more so than the national algorithm – and the AKI nursing team worked to remove any false positives. This interventional, quasi-experimental, longitudinal, before-and-after study generated significant improvements in AKI incidence (313 average new cases reduced to 215 cases per month, 2.5% reduction as proportion of admissions), on hospital-acquired AKI (28% reduction) and on length of stay (22.1 to 17 days, 23% reduction). There was also a trend toward improvements in mortality (average 38 deaths per month to 34 deaths per month).[13]

Meanwhile, the Liverpool team under Chandrasekar combined many of the above interventions, leading to a very different study designed. They introduced a new critical care based outreach team for all medically unwell patients and those with AKI and an additional risk prediction score that was in use prior to the improvement project. They saw an overall reduction in mortality rate (23.2% reduction for in-hospital mortality, 25.9% for 30 day mortality) sustained over 33 months, a reduction in AKI 3 and a reduction in length of stay (2.6 days).[13,16]

Other improvements seen as a product of the e-alert system are medication and pharmacy orientated. Several single centre studies (McCoy,[19] Terrel,[21] Claus[22] and Awdishu[23]) identified more appropriate dosing, increased use of contrast prophylaxis and improved rates and timeliness of medication. However, they did not evaluate the patient outcomes that are within the scope of this paper. Such interventions need further evaluation and may well have a clinically relevant impact for AKI.

It is important to recognise that while the e-alert is now mandatory for detection of AKI, the process of alerting the key staff to engage in clinical correlation remains flexible. The e-alert must therefore be appropriately supported with a tangible set of actions such as the AKI bundle, and buttressed with a dynamic and accessible programme of education, as described by Ebah and Chandrasekar in their differing but similarly effective quality improvement projects.[13]

1.5.2 AKI Care bundles

A care bundle is a collection of interventions grouped together to investigate and manage a specified condition. The International Healthcare Institute (IHI) definition of a 'care bundle' is shown in Figure 1-3.

Figure 1-3. The International Healthcare Institute (IHI) definition of a 'care bundle' [24]

"A structured method of improving processes of care and patient outcomes; a small, straight-forward set of evidence based practices, treatments and/or interventions for a defined patient segment or population and care setting that, when implemented collectively, significantly improves the reliability of care and patient outcomes beyond that expected when implemented individually.

- The bundle has 3–5 elements
- Each bundle element is relatively independent
- The bundle is utilized for a defined population in a defined location
- The bundle is developed by a multi-disciplinary team
- Each bundle element should be descriptive rather than prescriptive in nature, to enable local customization and applicable clinical judgment
- Compliance with bundles is measured as 'all-or-none' with an ideal target of greater than 95%"

The rationale for the use of care bundles is clear from the track record laid down by the 'Sepsis Six' campaign and the sepsis bundle. Introduction of the sepsis bundle has halved mortality (21.2% to 8.7%) in a multicentre observation US cohort of 4329 patients; this was correlated with increased bundle compliance (4.9% to 73.4%)[25]. However, for AKI, rates of implementation and bundle completion remain low. Nguyen, in a prospective cohort study of 556 patients from eight tertiary medical centres in Asia[26], noted that bundle compliance improved from 13% (baseline) to 54% following education and 4 cycles of quality improvement work (p=<0.01). Bundle completion equated to a relative risk reduction of death of 0.251 (95% confidence interval; 0.007 to 0.442). Steinmo [27] interviewed 34 medical professionals to explore barriers and influences on bundle compliance, allowing behavioural science to feed back into PDSA cycles and solve real-world care bundle application issues. There is a need to understand this phenomenon of improved outcome with relatively poor bundle completion compliance.

There is a growing body of evidence for the impact of the AKI care bundle that is summarised in Table 1-4. This table shows the outcome of the reviewed literature.

Tsui et al. published their single centre UK audit results of 108 patients that focused on educating junior doctors to complete the bundle. This served to improve documentation (p=<0.001) with a reduction in high dependency unit admissions (p=<0.001) and renal replacement therapy in the Intensive Care Unit (1.8% to 0%).[29] This study did not include hospital-acquired AKI, and acknowledged that junior doctors' documentation was insufficient to ensure adequate completion of the bundle. The study design lacked an MDT approach to educate and involve others in AKI management and there were small numbers of High Dependency and Intensive Care admissions..

The prospective observational study of over 2000 adults in the UK carried out by Kolhe et al.[15] found that timeliness was a significant factor in outcomes. The authors assert that completion of a care bundle within 24 hours of admission was associated with a significantly lower hazard ratio of death 0.771 (95% CI 0.620, 0.958) after a median follow-up of 134 days in comparison to those who did not have a care bundle completed within 24 hours (p=0.019). They did not however collect the data on which elements of the care bundle each patient received which may have contributed to the positive outcomes.

As discussed in the previous e-alert results section, Ebah and Chandrasekar[13,16] both used care bundles as part of their quality improvement project interventions. Bundle compliance was considered as part of the discussion in each study. Ebah in particular considers the individual elements and their compliance in an "unbundled" analysis. If the 10 elements of Ebah's bundle were "unbundled" there would be 90% compliance, as compliance with urine dipstick was poor.[13] Chandresekar, however, did not analyse compliance with the care bundles as part of the quality improvement project.[16]

Does compliance necessarily equate to improvement? Bhagwani's quality improvement project of an AKI sticker, educational intervention and AKI bundle, audited 92 patients and found that 62% had a fluid chart pre-AKI bundle. Compliance actually decreased with bundle introduction. This result was thought by the researchers to reflect the isolated education given only to junior doctors and not

the wider hospital staff, such as the nurses, who complete the fluid balance charts. Availability, awareness and accessibility of the physical bundle sticker also limited its use and the documented results.[30]

Joslin et al. audited 192 episodes of AKI care at a Central London hospital and found significant improvements in recognition, fluid assessment and nephrotoxic cessation (all p=<0.001) following introduction of their 8-element AKI bundle, but this was not correlated with improved patient outcomes.[31] Educational campaigns raise staff awareness, but significant complex external and human factors influence completion of bundles. As seen with the sepsis campaign, there is a constant need to assess and overcome barriers to implementation of the bundle to allow true evaluation of its impact.[32]

Table 1-4. Studies showing the effect of care bundles on AKI outcomes (adapted from Selby [28]).

Study	Size/type	Setting	Bundle	Outcome
Mortality				
Kolhe et al. 2015[15]	1209 pre CB 1291 post CB	Hospital	6 elements (fluid assessment, urinalysis, diagnose cause of AKI, order investigations, initiate treatment, refer)	Lower mortality p=0.045, lower progression of AKI 1 to 2/3 p=0.02
Ebah 2017[13]	Quality improvement project; interventional before and after study	Hospital pilot 1 ward, scale up 4 wards then hospital wide	10 point Priority care checklist (baseline, cause, fluid assessment, cause and investigations, catheter, USS, renal referral, fluid balance, urine dip, drug review)	Trend towards lower mortality 34 per month, vs 38 per month prior to intervention

Chandrasekar 2016[16]	Quality improvement project interventional study	Hospital	ABCDE-IT (Acute complications, Blood pressure, Catheterise, Drugs, Exclude obstruction, Investigations, Treat cause	23.2% reduction in in-hospital mortality 25.9% reduction in 30-day mortality sustained over 33 months
Kolhe et al. 2016[28]	3518 (939 with CB, 1823 without)	Hospital	6 elements (fluid assessment, urinalysis, diagnose cause of AKI, order investigations, initiate treatment, refer)	Lower mortality (20.4 vs. 24.4%, p = 0.017)
AKI progression, creatinine rise or dialysis incidence				
Tsui et al. 2014[29]	55 patients pre and 53 post CB	Hospital	11 elements (baseline creatinine, fluid status, urinalysis, med review x 2, u PCR, urine output, renal USS, referral x 3)	Reduction in RRT in ICU 1.8% to 0% Reduction in HDU p=<0.001, better documentation p=<0.001
Kolhe et al. 2016[28]	3518 (939 with CB, 1823 without)	Hospital	6 elements (fluid assessment, urinalysis, diagnose cause of AKI, order investigations, initiate treatment, refer)	less AKI progression (4.2 vs. 6.7%, p = 0.02)
Chandrasekar 2016[16]	Quality improvement project interventional study	Hospital	ABCDE-IT (Acute complications, Blood pressure, Catheterise, Drugs,	Weak inverse correlation of AKI incidence (R^2 0.351), decrease in AKI 3 and decrease length of stay (2.6 days)

			Exclude obstruction, Investigations, Treat cause	

OR=odds ratio; CB=care bundle; u PCR=urine protein: creatinine ratio; RRT= renal replacement therapy

1.5.3 Educational packages

There is little research concentrating on the effect of education on outcomes in AKI, and none of it met the inclusion criteria for this review. Ebah and Chandrasekar each credit education as a contributor to the results seen in their respective quality improvement projects, with Ebah referring to a well-received and effective 4-slide headline tool.[13,16]

Gang Xu et al. have completed a two centre UK-based study looking at an educational package to improve outcomes in AKI. There were 319 questionnaires completed by physicians pre-intervention and 138 post-intervention. Their work improved awareness of AKI guidelines from 26% to 64% (p=<0.001), self-reported diagnosis of AKI (50% vs. 68%, p=<0.001) and investigating AKI (48% vs. 64%, p=0.002).[33]

It is difficult to discern individual educational packages' effects or impacts in isolation from other interventions, as it is implicit that a change such as an e-alert would require supporting information and education. Selby[14] maintains that the effect lies in a triad of strategies:

1. Detailed, bespoke education
2. Electronic detection and e-alerts
3. Care bundle

1.5.4 AKI nurses and AKI outreach teams

Different approaches to responsibility for AKI are adopted in different centres, with some considering AKI the responsibility of nephrologists, whereas others consider AKI to be everyone's problem.[3] AKI specialist nurses are a growing factor in the interventions developed to tackle AKI. The nurses can provide targeted education to

those wards with high prevalence in an opportunistic manner and create a redundancy in the system so that patients with AKI are not missed.

Thomas[11] described a phone call-based outreach service in a single UK centre (as discussed in the e-alert results section) which, overall, generated more recommendations but garnered no statistical improvements. There is a delicate balance between improved AKI outcomes and increased work for radiology, nephrology and pathology colleagues. Gulliford[34] whose work covers three district general hospital settings within the UK, saw an increase in renal USS, renal review and senior review, but also saw better medication prescribing, less AKI 3, decreased LOS and decreased mortality.

Royal Liverpool University Hospitals combined several methods utilised elsewhere and introduced an AKI team and AKI risk scoring system. There has been a reduction in AKI progression and an 18% reduction in median hospital mortality. This has been achieved by combining an outreach team review for medically unwell patients with a bleep system for those scoring on the early warning system and prompt intervention and review.[35]

The MAKIT better study[36] and Ebah[13] at the Central Manchester Foundation Trust both describe how the introduction of two AKI nurses led to improvements in several of the key areas. Ebah's study is described in the results section and the MAKIT better study saw similar results with regards to AKI incidence (18% reduction), hospital acquired AKI (1% reduction), mortality (10% reduction) and length of stay (10% reduction), although it is not stated whether these were statistically significant.

These appear to be showing a trend towards improvement. It may be that a combination of dedicated nurse time, "an extra pair of hands" assistance by outreach to give timely intervention, education and human interaction is more persuasive than an inanimate e-alert. A summary of these findings is found in Table 1-5.

Table 1-5. Studies showing the effect of AKI nurses and AKI outreach teams on AKI outcomes

Author	Intervention	Outcome
Thomas[11]	Outreach service	More recommendations made, initial 6% improvement in mortality, no statistical improvements long term
Hill[37]	AKI/outreach team – review AKI 2/3 and EWS scores >5	Less AKI progression, 18% reduction in median hospital mortality
CMFT MAKIT[36]	AKI nurses, e-alerts, education	Decrease hospital acquired AKI (-1%), decrease mortality (-10%)
Gulliford[34]	AKI nurse, education, AKI champions, telephone follow up	Less AKI 3, decreased mortality
Chandrasekar[16]	Outreach team/AKI nurse, care bundle, e-alerts, education	Weak inverse correlation of AKI incidence (R^2 0.351), decrease in AKI 3 and decrease length of stay (2.6 days)
Ebah[13]	AKI nurses, e-alerts, education, care bundle	Decrease in AKI incidence (9 to 6.5%), decreased length of stay (22.1 to 17 days), trend towards improvement in mortality

1.5.5 Smartphone applications, AKI app

Smartphones are now almost ubiquitous in hospital throughout both the general public and medical professionals, allowing immediate access to information at the point of care. Despite several AKI related apps from London, Edinburgh, Salford (AKI care) and Leeds (RRAPID - sepsis based) there is no data yet on their effectiveness or impact. As this intervention remains isolated from the NHS IT services, it is likely that mostly it will serve as an educational and reference tool. With the advent of Google and DeepMind integration at the Royal Free in London we await analysis from projects that may lead to developments in the future. This is discussed further in Chapters 7 and 9.

1.5.6 Sick day guidance

There is no published quantitative evidence or long-term data on sick day guidance and its impact on AKI outcomes. The hypothesis for sick day guidance is that reducing or omitting medications such as anti-hypertensives or diuretics during an

intercurrent illness will lead to a reduction in AKI incidence or progression. However this hypothesis has struggled from its conception. The main issue is a lack of consensus between renal and other specialities as there is little evidence to support this intervention thus undermining confidence in the premise. Heterogeneous groups of patients sustain AKI. As such, no "one size fits all" message is suitable. This is the key point in the qualitative piece by Morris et al. exploring the implementation of sick day guidance in primary care in the North West of England.[38]

Several studies clearly indicate that combination medication such as angiotensin-converting enzyme (ACE-inhibitors), diuretics and non-steroidal anti-inflammatories (NSAIDs) are a risk for AKI. Tomlinson,[39] found an increased prevalence of AKI in those on ACE inhibitors and angiotensin receptor blockade (ARB) over a 4 year study period from an observational study of around 8000 general practices across the UK. Likewise, Lapi[40] performed a similar nested case-control study of over 487, 000 patients, with 2215 episodes of AKI, and found that a triple combination of diuretics, ACE inhibitors and NSAIDs increased incidence of AKI (rate ratio 1.31, 95% CI 1.12 to 1.53). There are professional consensus opinions published by the collaborative Think Kidneys Board[41] yet overall there is a need for improved resourcing and evidence base [38].

1.6 Discussion

The NCEPOD of 2009 has been a great motivator by creating improved public awareness of AKI, increasing its profile in the NHS, and by provoking the introduction of financial incentives. This narrative review supports the growing body of evidence that grouped interventions can create an impact on the progression and severity of, and mortality from, AKI. Overall success appears to be due to a combination approach of an e-alert and an AKI bundle, supported by overarching education and an AKI nurse to create a failsafe within the system.

- The e-alert must be timely and appropriately intrusive to trigger actions such as the completion of an AKI bundle.

- All healthcare workers, from healthcare assistants, nurses and doctors both undergraduate and postgraduate, should undergo AKI education with a focus on risk recognition, the unwell patient and task prioritisation.

- There must be a redundancy built into the system, be it AKI nurses or dedicated pharmacist review, to mitigate for human factors and ensure that alerts translate into action.

1.6.1 Where does the AKI community look to next?

At present the system is entirely reactive. For example, e-alerts and care bundles only commence once the insult has happened. In order to reduce AKI incidence there is a need for a proactive element. Successful and reliable risk modelling for AKI, coupled with education and rapid recognition of the deteriorating patient, may well result in an impact on incidence.

NCEPOD's report "Adding insult to Injury'[1] suggests that simple achievable change lies in ensuring that the basics of patient monitoring and investigations are completed, then escalated, in a timely and appropriate fashion. This would include identification of, and early intervention for, those at high risk of AKI.[1] This will probably rely on further research and a public and health sector wide programme of education.

A separate key intervention concerns feedback mechanisms between secondary and primary care. Dissemination of information from in-hospital patient stays or visits, such as discharge summaries and clinic letters, must improve in both quality and consistency, as must corresponding coding practices in primary care. The most discernible predictive factor for AKI is having had one previously. A patient who has had an AKI already has composite risk factors for AKI recurrence. Flagging up each patient with an AKI on discharge for review of these risk factors in the community should trigger consideration of secondary prevention.

Machine learning approaches to detection of AKI are emerging through collaboration between the Royal Free in London and GoogleMind. They show promise in more severe cases of AKI detection however are in a select cohort and are yet to be validated in a secondary cohort or within another healthcare setting or system.[56] This is further discussed in Chapter 9.

Compliance with ethical standards

Authors: Dr Sykes, Dr Nipah, Professor Kalra and Dr Green

Conflict of interest: The authors declare they have no conflict of interest.

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Chapter 2

Methodology

2.1 Rationale

This is a generic methods chapter describing an overview of the methods used throughout this PhD. Due to the significantly varied methods used in different analyses, from varied statistical methodologies and quantitative data analysis to quality improvement methodology, this chapter will address broad concepts only. The subsequent individual results chapters provide in depth detail of the specific methods used for the studies they describe.

2.2 Setting and patient population

Salford Royal NHS Foundation Trust is a tertiary referral centre for renal services and neurosciences. It has over 800 acute in-patient beds that serve a population of 220,000 directly and a catchment area of 3.5million in the Greater Manchester area, for which it supplies approximately 50% with renal services. It is a national centre for intestinal failure patients and those with metabolic diseases. Acute trauma services are shared across the Manchester region; Salford Royal Foundation Hospital receives neurosurgical trauma patients, University Hospital South Manchester receives cardiothoracic trauma patients and Manchester Royal infirmary receives vascular trauma patients. Neighbouring Trusts provide vascular services and cardiac catheterization services.

The City of Salford is in the 20% most deprived areas in England. The local population has a high proportion of permanently sick or disabled patients (6.7%) in comparison with the national average (4%). It is a predominantly white area (86%), with 5% Asian and 4.6% black populations. It has a significantly worse all cause morbidity, cardiovascular and cancer rate in the under 75s than the rest of England. It also has significantly high rates of self-harm, alcohol and smoking compared to

the rest of England. Average life expectancy for Salford residents is 2.7 years less than for the average of England as a whole, according to Public Health England 'Salford Health Profile 2018'.[1]

2.3 Data pull and processing

Salford Royal is a Global Digital Exemplar site and exhibits high levels of digital maturity. It has a long history of electronic patient records (EPR) and has established links to the community and primary care electronic services. Therefore there is a vast volume and granularity of data that can be harvested from where this is stored in the Trust's secure digital "data warehouse".

The data warehouse provided the majority of the raw data used for this PhD. It was accessed through our information management and technology team's data analysts. All of the Salford Royal Hospital and surrounding services' pathology results are available to access via an SQL (structured query language) database. Through multiple discussions and iterations we developed SQL to pull specific data from the warehouse. The Information management and technology team were able to write a report to identify the data items needed for the indicators for each project. These data were pulled into Qlikview (Qlik, Pensylvania, USA), a reporting tool that is accessible from within the Trust network. These data were anonymised prior to any download to comply with data protection rules. Throughout all of the thesis projects, no patient identifiable information was ever used.

The only data that were used in this thesis but not accessed directly via the Trust were the data for analysis of the 'AKI Care app' in chapter 7.[2] This work was undertaken following a data pull of the background user details and data from within the app itself. Given that no prior permission had been given to use this data to contact app users regarding their experience and preferences within the app this was also anonymised.

2.4 Salford Kidney Study

The Salford Kidney Study (SKS) is a longstanding, prospectively collected, longitudinal study of outcome sin chronic kidney disease and acute kidney injury. SKS is undertaken solely at the Salford Royal Hospital site. Patients from the SKS

were included in analyses in results chapter 5.[3] The SKS obtains demographic and clinical information at study entry and thereafter on an annual basis. Trained research nurses through a structured patient questionnaire deliver this. Reported co-morbidities and health issues are validated by reference to clinical notes stored within EPR, through communication with their primary care provider, or by other secondary care providers in cases where admission to outlying hospitals occurred. All patients have a standardised biochemical and haematological analysis performed on an annual basis. Additional laboratory data collected as part of routine clinical care are also available for analysis. Data from SKS are stored on a secure serer at the Trust and, as with all data from Salford Royal used in this thesis, was extracted anonymously prior to analysis in line with Trust data protection policy and the SKS ethics approval.

2.5 Acute kidney injury definition

In this PhD episodes of AKI were retrospectively identified according to the KDIGO (Kidney Diseases Improving Global Outcomes)[4] definition of AKI, using the national algorithm.[5] The algorithm was also retrospectively applied to creatinine measurements historical to the mandatory introduction of the national AKI e-alert to include our data entries from 2011. It therefore includes analysis of all available repeated measurements of serum creatinine in each patient. Measurement of urine output for the extended KDIGO criteria was not available for consideration and was not included in any of the studies due to lack of reliability of monitoring, completeness and the referred nature of the population from both community and other hospitals.

The stage of an AKI episode was defined according to the criteria listed below. The relative change (RC) in serum creatinine (SCr) between two successive measurements (t and s) was calculated according to $(SCr_t - SCr_s)/(SCr_s)$. The classification of AKI episodes was as follows:

- Stage 1: $0.5 \leqslant RC < 1$ or an absolute increase in SCr $\geq$ 26.5 μmol/L;
- Stage 2: $1 \leqslant RC < 2$
- Stage 3: $RC > 2$ or SCr $\geq$ 353.6 μmol/L or initiation of renal replacement therapy

2.6 Biochemical data

The samples were analysed in Salford Royal Foundation Trust pathology laboratories. A range of multidisciplinary staff took the samples. The trust has mandatory aseptic non-touch technique (ANTT) training annually with procedure based competencies assessed at induction. The method of collection of each phlebotomy sample varied as it may be a direct vessel puncture with a needle and vacutainer or via cannula. The samples were then homogenized by gently agitating. The serum samples in hospital are then sent in a pod via a pneumatic air system to the laboratory or sent by taxi courier in from the community.

The serum blood samples were analysed on the automatic analysers in the laboratory. The central pathology laboratory of the Trust provides biochemistry services for all inpatient and outpatient venous samples, including those taken in a primary care setting. From March 2011 until January 2015, a compensated kinetic Jaffe method with an inter-assay coefficient of variance of 1.7% at 193 μmol/L (Roche Cobas 8000) was used to measure all serum creatinine values (normal creatinine range, male: 62-106 μmol/L; female: 44-80 μmol/L). From January 2015 to December 2017 the method was a compensated kinetic Jaffe method with an inter-assay coefficient of variance of 2.9% at 156 μmol/L (Siemens, Advia) (normal creatinine range, male: 62-115 μmol/L; female: 44-97 μmol/L). The analysers both use Jaffe-compensated and enzymatic analysis and therefore unlikely to provide significantly different results and no statistical alteration was made after the change of analysers.

2.7 Quality improvement methodology

The International Health Institutes (IHI) Breakthrough collaborative series model was used for Chapter 6 due to the hospital Trust's extensive previous experience with this methodology.[6] This meant that the quality improvement team based at Salford Royal was able to support the design and execution of this project with their expertise and resources.

2.8 Statistical analyses

All of the analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) version 23 for Mac [SPSS (UK) Ltd, Woking, Surrey, UK]. There are multiple different approaches used within this PhD to analyse the data and to generate results. Within each chapter the specifics of the data analysis can be found.

2.9 Ethics

Access to the data warehouse was granted by the Trust Caldecott Guardian for the purposes of quality improvement and research. The data was used to identify specific targets for quality improvement work within the Trust tackling acute kidney injury. It was further used to measure and monitor the effect of both AKI itself and any interventions placed. As this was a quality improvement (QI) study using anonymised data collection for both analysis and reporting, it is exempt from specific ethical approval.

Ethics for the Salford kidney study (SKS) was granted by the South Manchester Ethics Committee. (current REC reference 15/NW/0818, North West - Greater Manchester South Research Ethics Committee)

2.10 References

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Chapter 3

Comparison of impact on death and critical care admission of Acute Kidney Injury between common medical and surgical diagnoses

3.1 Rationale

This chapter investigates the incidence and clinical impact that that an acute kidney injury (AKI) poses to a patient admitted to hospital, relative to patients without AKI, and comparing whether this impact is the same across different admission reasons. This study used "big data" to understand, in greater depth than previous research, how AKI can be a marker of significantly increased risk for critical care admission and mortality. Through accessing the rust data warehouse, significant numbers of patient episodes could be described in detail allowing pooling of patient admission reasons during statistical analysis. This was explored in eight of the most common medical and eight common surgical diagnoses. This work identified areas of high AKI incidence but also of high severity of AKI and therefore gave specific targets to the quality improvement collaborative work seen later in chapter 6.

This work has already been published in PLOS and presented at SAMDAM (the Society of acute medicine and Dutch acute medicine) in Amsterdam.
PLOS DOI: 10.1371/journal.pone.0215105

3.2 Abstract

Background

Acute Kidney Injury (AKI) is common and associated with increased morbidity and mortality. This retrospective analysis quantified and compared the association between AKI and the risk of death and admission to critical care in acute admissions of different aetiology.

Methods

Data were extracted anonymously from the Trust 'data warehouse' for admissions between 2011and 2017. We applied KDIGO AKI criteria to establish AKI stage. Odds ratios (OR) for death and critical care admission were calculated for patients with AKI stage 3 (compared to all other patients), and patients with any stage AKI (compared to non-AKI admissions). Analyses were performed using logistic regression, adjusted for age, pre-existing CKD, co-morbid index, and gender.

Results

There were 26,052 medical and 12,560 surgical patient episodes within sixteen common diagnoses with 3823 medical and 1520 surgical patients with AKI events. The likelihood of AKI was highest in sepsis (31.8%), and the likelihood of death in AKI 3 highest in femoral neck fracture (54.5%). AKI 3 has a OR for death for acute coronary syndrome of 12.8 and a OR of 24.6 in femoral neck fracture. Admission to critical care for any AKI in medical patients has a OR of 9.6, but increases to OR 37.2 for heart failure.

Conclusion

The clinical impact of AKI differs across medical and surgical diagnoses, but is a significant contributor to the risk for death and critical care admission. This body of work may indicate a benefit to a more diagnosis-specific stratified approach to AKI care.

3.3 Background

Acute Kidney Injury (AKI) is a common and serious condition that is associated with increased morbidity and mortality.[1–3] It is not a disease but rather a syndrome and a reflection of the severity of an illness affecting a patient.[4] Increasingly

therefore, AKI can be used as an 'illness barometer' for patients. An episode of AKI has strong associations with increased length of stay, mortality, level of care, and specialty input required over the course of admission.[5–7]

AKI affects a wide range of patients both within hospital and in primary care. The incidence of AKI in hospital under different specialty teams (excepting nephrology) is highest in medicine for the elderly, cardiology, general surgery and gastroenterology. Within the NHS AKI cases are managed by the specialty team managing the main medical or surgical condition rather than specifically by nephrologists[8], although the latter do supervise the care of patients with the more severe AKI episodes.

Previous studies into AKI in different specialties have used the admitting specialty as an umbrella proxy to categorize patients into groups, and as such may lack the granularity to understand patient complexity and confounders such as specific diagnoses and co-morbidities.[9,10] This latter consideration may be vital because diagnosis is likely to be more accurate than the umbrella parent specialty in stratifying individual patient risk associated with an AKI episode.

The aim of this study was to quantify and compare AKI epidemiology in secondary care between specific common medical and surgical diagnoses. The intent was to evaluate not only the incidence of AKI, but also the impact that AKI has on outcomes after hospital admission, specifically death and critical care admission. Such information may allow adoption of a more patient-specific, stratified approach to AKI care by recognizing that the prognosis after AKI will differ between diagnoses.

3.4 Methods

3.4.1 Setting

The population and demographics of Salford are described in the generic methods chapter.

3.4.2 Data

Data for all non-elective inpatient episodes at Salford Royal between 1st March 2011 and 31st December 2017 were extracted anonymously from the Trust 'data warehouse'. Salford Royal is a global digital exemplar site and data extraction relating to patient episodes could be performed with complete patient anonymization and with a high level of granularity for event data. Data extraction was performed as part of an AKI quality improvement initiative. This was exempt from specific ethical approval as it was anonymised data. [11]

Data extracted were date of admission, length of stay, critical care admission, age, gender, ICD-10 codes for admission diagnosis and co-morbidities, inpatient mortality, dialysis episodes, and laboratory data for serum creatinine values. The 8 most common acute medical and surgical admission diagnoses were selected based on ICD-10 codes determined after discharge, and are shown in Table 3-1. In order to acknowledge that some patients have more than one diagnosis during admission, patients were grouped according to their coded main diagnosis. Patients admitted with other diagnoses were excluded, as were patients already established on maintenance dialysis therapy or those who had a functioning renal transplant.

Table 3-1. The 8 most common medical and surgical diagnosis categories and their relative frequency amongst all admissions

Medical			Surgical		
Key	**Diagnosis**	**Frequency %**	**Key**	**Diagnosis**	**Frequency %**
CAP	Community acquired pneumonia	3.6	**NTICB**	Non Traumatic Intra Cranial Bleed	1.4
UTI	Urinary tract infection	2.4	**Chole**	Cholecystitis/ cholangitis	1.1
ACS	Acute coronary syndrome	2.1	**TICB**	Traumatic Intra Cranial Bleed	1.0
COPD	Chronic obstructive pulmonary disease	2.1	**NOF**	Femoral neck fracture (NOF)	0.9
GIB	Gastro-intestinal bleed	0.8	**Abscess**	Abscess (any site)	0.7
HF	Heart failure	0.8	**Panc**	Acute pancreatitis	0.5
Sepsis	Sepsis (any source)	0.8	**Appendix**	Acute appendicitis	0.3
ALD	Alcoholic liver disease	0.3	**ENT**	ENT (ears, nose and throat) (any source)	0.3

The Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria[12] were manually applied retrospectively using the National AKI algorithm[13] to available creatinine measurements to determine AKI episodes during each admission, and to establish AKI stage.

3.4.3 Statistical analysis

Groups of patients were selected by their primary admission diagnosis with the 8 most common medical and surgical diagnoses selected for inclusion. A comparison of patient characteristics was then made between medical patients with diagnoses selected for inclusion in the study, surgical patients with diagnoses selected for inclusion in the study, and the remainder of admissions during the study period, except for those fitting exclusion criteria as detailed above. Inter-group comparison

of binary variables was performed using chi-square tests and comparison of continuous variables was performed using one-way ANOVA.

For each selected medical and surgical admission diagnosis, Odds ratios (OR) were calculated for inpatient death and for admission to critical care after AKI onset in patients with AKI stage 3 compared to other patients, including those with lesser stages of AKI. The analyses were repeated comparing outcomes for patients with any stage of AKI in comparison to admissions without AKI for that specific diagnosis.

All of the analyses were performed using logistic regression, adjusted for age, pre-existing chronic kidney disease (CKD), co-morbid index, and gender. IBM Statistical Package for the Social Sciences (SPSS) version 23 for Mac [SPSS (UK) Ltd, Woking, Surrey, UK] was used for analyses.

3.5 Results

3.5.1 Study population

Between March 2011 and December 2017 (80 months) there were 197,884 non-elective inpatient episodes. Of these, 26,052 (13.2%) fell within the 8 selected medical diagnoses, and 12,560 (6.3%) within the 8 selected surgical diagnoses. The most common medical diagnosis was community-acquired pneumonia (n = 7,323), which accounted for 3.6% of all hospital admissions during the study period. The most common surgical diagnosis was non-traumatic intracranial bleed (NTICB, n = 2,831), which accounted for 1.4% of admissions. Overall, the selected medical and surgical diagnoses accounted for 19.1% of all hospital admissions during the study period. Full details of the selected diagnoses and their frequencies are found in Table 3-1.

The split between male and female patients in the medical and surgical selected diagnoses (both 52% female) was more even than in the rest of the acute admission population (57% female). The selected medical population had a higher mean age, number of co-morbidities, CKD incidence, AKI and AKI 3 incidence, mortality, and critical care admission than both the overall acute admission population and selected surgical population. The selected surgical population was older, had a higher number

of comorbidities, AKI incidence and death rate than the overall acute admission population, but lower AKI 3 incidence. Full details of comparisons between the selected and whole populations are found in Table 3-2.

Table 3-2. Demographics of the selected medical and surgical diagnoses in comparison to the overall admission population

Demographic	Overall	Medical selected diagnoses	Surgical selected diagnoses
Patients	197,884	26,052 (13.2%)	12,560 (6.3%)
Male gender (%)	85,090 (43%)	12,558 (48%)	6076 (48%)
Age mean (SD)	55.5 (22.3)	69.8 (16.9)	57.3 (21.7)
CKD (%)	17,262 (8.7%)	3283 (12.6%)	545 (4.3%)
Comorbidities (range)	6.9 (1-17)	9.6 (1-17)	8.3 (2-17)
Any AKI (%)	15,217 (7.7%)	3823 (14.7%)	1520 (12.1%)
AKI 3 (%)	5740 (2.9%)	638 (2.4%)	85 (0.7%)
Death (%)	6749 (3.4%)	2292 (8.8%)	974 (7.8%)
Critical care (%)	9001 (4.5)%	606 (2.3%)	1852 (14.0%)

3.5.2 Event counts for Acute Kidney Injury by medical and surgical diagnosis

In the whole acute admission population there were 197,884 patient episodes with 15,218 AKI events (7.7%) as shown in Table 3-3. There were 26,052 patient episodes within the 8 selected medical diagnoses, with 3,823 (25.1%) AKI events. There were 638 (4.2% of the whole pop, 16.7% of the medical AKIs) AKI stage 3 events. The likelihood of any AKI was highest in sepsis (31.8%), and lowest in acute coronary syndrome (ACS, 6.0%). The likelihood of AKI 3 was highest in sepsis (6.9%) and alcoholic liver disease (ALD, 6.2%). The likelihood of any AKI was lowest in acute coronary syndrome (ACS, 6.0%) and COPD (7.7% As a proportion of AKI events, AKI 3 events were most likely in ALD (26.3% of AKI events, see Figure 3-1), and least likely in ACS (9.4%) and COPD (9.3%). Figure 3-1 also shows that as the risk of any AKI increased in medical diagnoses, the risk for AKI 3 also proportionately increased.

Table 3-3. Event counts for Acute Kidney Injury by medical and surgical diagnosis

Diagnosis	N	AKI 3			Any AKI	
		N	% AKI	% cases	N	% cases
Medical						
CAP	7232	203	16.2	2.8	1253	17.3
UTI	4800	147	18.2	3.1	808	16.8
ACS	4266	24	9.4	0.6	255	6.0
COPD	4234	30	9.3	0.7	324	7.7
Sepsis	1672	116	21.8	6.9	532	31.8
HF	1652	57	16.5	3.5	346	20.9
GIB	1615	25	16.4	1.5	152	9.4
ALD	581	36	23.5	6.2	153	26.3
Overall	26052	638	16.7	2.4	3823	14.7
Surgical						
NTICB	2830	18	3.5	0.6	518	18.3
Chole	2261	24	9.9	1.1	242	10.1
TICB	2026	8	2.8	0.4	282	13.9
NOF	1815	22	6.6	1.2	332	18.3
Abscess	1352	1	5.2	0.1	19	1.4
Panc	936	9	9.6	0.1	94	10.0
Appendix	683	1	4.2	0.1	24	3.5
ENT	657	2	22.2	0.3	9	1.4
Overall	12560	85	5.6	0.7	1520	12.1

Table key: % AKI = percent of AKI events that were AKI 3, % cases = % of patients with selected diagnosis who had AKI 3 / any AKI.
ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community acquired pneumonia, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, HF – heart failure, sepsis – sepsis (any source), UTI – urinary tract infection. Abscess – abscess (any source), appendix - acute appendicitis, Chole - Cholecystitis/cholangitis, ENT (ear, nose and throat) – ENT (any source), NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed, Panc - acute pancreatitis, TICB - Traumatic Intra Cranial Bleed.

Figure 3-1. Percentage of patients with any acute kidney injury (AKI) or AKI 3 in each medical diagnosis, ordered by increasing frequency of AKI

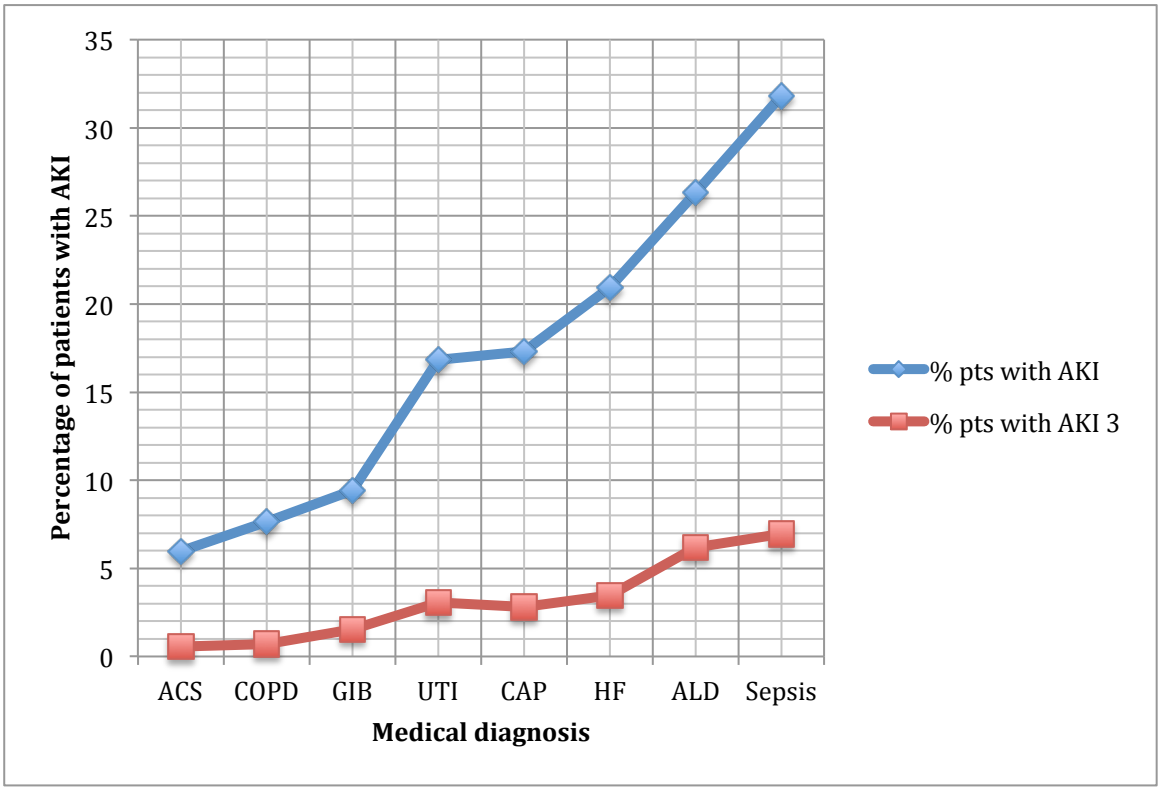

Figure key: ACS – acute coronary syndrome, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, UTI – urinary tract infection, CAP – community acquired pneumonia, HF – heart failure, ALD – alcoholic liver disease, sepsis – sepsis (any source). % pts with AKI = percentage of patients with each diagnosis with AKI or AKI 3

There were 12,560 patient episodes within the 8 selected surgical diagnoses, with 1,520 (10.0%) AKI events. There were 85 AKI stage 3 events (0.6% of the overall population AKIs, 5.6% of the surgical diagnoses). Overall, surgical diagnoses were less likely to manifest AKI than medical diagnoses. Of the 8 diagnoses in which an AKI was most likely, only 2 were surgical diagnoses. For AKI 3, only 1 of the 8 diagnoses in which AKI 3 occurred most frequently was a surgical diagnosis.

The likelihood of any AKI was highest in femoral neck fracture and NTICB (18.3% in both patient groups). The likelihood of AKI 3 was highest in femoral neck fracture (1.2%) and cholecystitis or cholangitis (1.1%). As a proportion of AKI events, patients with ENT diagnoses and pancreatitis were most likely to have AKI 3 (22.2% and 9.6% of admissions respectively). This data is, however, skewed by small

numbers, as there were 2 AKI 3 events in 9 patients for ENT admissions, and 9 AKI 3 events for 94 pancreatitis admissions. The lowest incidence of any AKI occurred in patients with abscesses and ENT diagnoses. AKI 3 events were lowest in traumatic and non-traumatic intracranial bleeds (2.8% and 3.5% of admissions respectively). Unlike for medical diagnoses, as the risk of any AKI increased in surgical diagnoses, there was no corresponding increase in the likelihood of AKI 3. AKI 3 occurred in less than 2% of patients in all surgical diagnoses (Figure 3-2). Are these therefore less severe episodes of AKI with different prognoses for recovery?

Figure 3-2. Percentage of patients with any acute kidney injury (AKI) or AKI 3 in each surgical diagnosis, ordered by increasing frequency of AKI

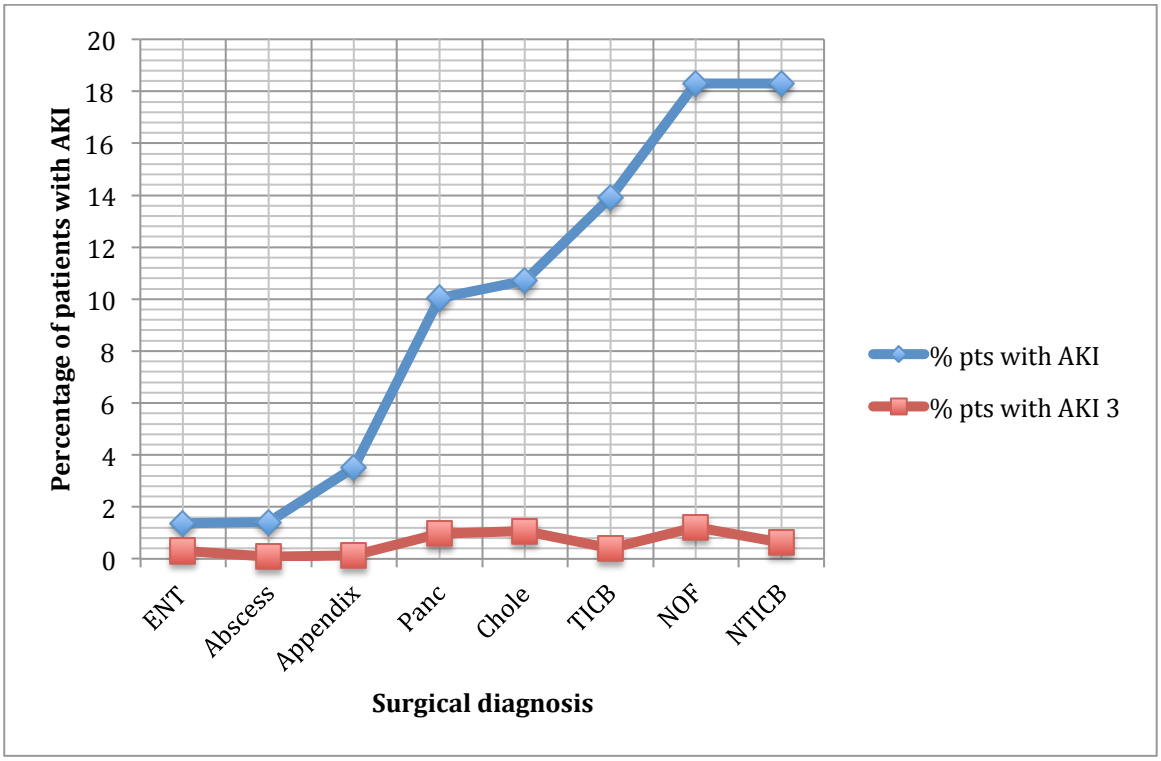

Figure key: ENT (ear, nose and throat) – ENT (any source), abscess – abscess (any source), appendix - acute appendicitis, Panc - acute pancreatitis, Chole - Cholecystitis/cholangitis, TICB - Traumatic Intra Cranial Bleed, NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed. % pts with AKI = percentage of patients with each diagnosis with AKI or AKI 3

3.5.3 AKI associated mortality

Overall mortality in the 8 chosen medical diagnoses was 5.1%, but there was a 5 fold increase to 27.7% for mortality with any AKI, and an 8 fold increase to 42.6% if an AKI 3 supervened. In comparison, the surgical incidence of mortality was lower, with a 1.9% overall mortality, 13.7% mortality in any AKI, and 29.4% mortality in AKI 3.

For medical diagnoses, the likelihood of death in any AKI was highest in community-acquired pneumonia (37.8%, compared with 8% for all community-acquired pneumonia), followed by sepsis (32.7%, compared with 14% for all sepsis patients). Mortality was lowest in any AKI in UTI (12.7%) and gastrointestinal bleed (17.8%). The likelihood of death in AKI 3 was highest in ALD (52.8%), followed by CAP (52.7%). The lowest risk of death in AKI 3 was also UTI (24.5%) and gastrointestinal bleed (28.0%).

For surgical diagnoses, the likelihood of death with and without AKI was generally lower than for medical diagnosis (any AKI 13.7% versus 27.7%, AKI 3 29.4% versus 42.6%). The likelihood of death in any AKI was highest in femoral neck fracture (18.4%), followed by traumatic intracranial bleed (TICB, 16.7%). Mortality was lowest in appendix and ENT surgery, where there were no deaths in either group. In diagnoses where deaths did occur, the lowest risk of death for any AKI was in patients with abscesses (5.3%). The likelihood of death in AKI 3 was highest in femoral neck fracture (54.5%), higher than in any medical diagnosis. The next highest likelihood of death in AKI 3 was in cholecystitis (29.2%). The lowest risk of death in diagnoses where deaths occurred was in TICB (12.5%) and NTICB (16.6%). A comparison of all mortality event rates across all medical and surgical diagnoses is found in Table 3-4, which includes mortality in the overall population for each diagnosis as a comparator.

Table 3-4. Event counts for death in medical and surgical admissions with AKI

Diagnosis	Total	All patients		AKI 3		Any AKI	
		N	%	N	%	N	%
Medical							
ACS	4266	63	1.5	8	33.3	55	21.6
ALD	581	59	10.2	19	52.8	40	26.1
CAP	7232	581	8.0	107	52.7	474	37.8
COPD	4234	91	2.1	15	50.0	76	23.5
GIB	1615	34	2.1	7	28.0	27	17.8
HF	1652	137	8.3	27	47.4	110	31.8
Sepsis	1672	227	13.6	53	45.7	174	32.7
UTI	4800	139	2.9	36	24.5	103	12.7
Overall	26052	1331	5.1	272	42.6	1059	27.7
Surgical							
Abscess	1352	1	0.1	0	-	1	5.3
Appendix	683	0	-	0	-	0	-
Chole	2261	31	1.4	7	29.2	24	9.9
ENT	657	0	-	0	-	0	-
NOF	1815	73	4.0	12	54.5	61	18.4
NTICB	2830	71	2.5	3	16.6	68	13.1
Panc	936	9	1.0	2	22.2	7	7.4
TICB	2026	48	2.4	1	12.5	47	16.7
Overall	12560	233	1.9	25	29.4	208	13.7

Table key: % AKI = percent of AKI events that were AKI 3, % cases = % of patients with selected diagnosis who had AKI 3 / any AKI.
ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community acquired pneumonia, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, HF – heart failure, sepsis – sepsis (any source), UTI – urinary tract infection. Abscess – abscess (any source), appendix - acute appendicitis, Chole - Cholecystitis/cholangitis, ENT (ear, nose and throat) – ENT (any source), NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed, Panc - acute pancreatitis, TICB - Traumatic Intra Cranial Bleed.

Any AKI in medical admissions conveyed an adjusted OR of 4.7 (95% confidence intervals 4.3 - 5.2, p<0.001) for death compared to patients without AKI. AKI 3 had a OR of 6.2 (5.2 - 7.4, p<0.001) in comparison to patients with either AKI 1, AKI 2, or no AKI. In medical diagnoses, the highest increased risk for death in any AKI compared to no AKI was in acute coronary syndrome (ACS, 8.9 [5.8- 13.5, p<0.001]), followed by heart failure (6.0 [4.3 – 8.4, p<0.001]). In AKI 3, the highest increased risk for death compared to all other patients was in ACS (12.8 [4.8 – 33.8, p<0.001]), and COPD (11.3 [5.1 – 24.4, p<0.001]). In medical diagnoses the lowest increase in risk for death in any AKI compared to no AKI was ALD (OR 3.0[1.7 – 5.2, p<0.001]) and sepsis (3.5 [2.6 – 4.6, p<0.001]). These were the medical diagnoses with the highest overall mortality (10% and 14% respectively) and the lower ORs here likely reflect the higher baseline mortality for these. For AKI 3, compared to all other patients, the lowest increase risk for death was again found in sepsis (4.2 [2.7 – 6.4, p<0.001]).

Any AKI in surgical diagnoses conveyed an adjusted OR of 1.8 (95% confidence intervals 1.5 – 2.1, p<0.001) for death in comparison to patients without AKI. In the selected surgical diagnoses, the highest risk for death in any AKI was in pancreatitis (OR 9.7 [2.5 – 37.4, p=0.001]), which is significantly higher than the other surgical diagnoses and higher than any of the medical diagnoses. AKI 3 in the surgical diagnoses had a OR of 4.0 (2.4 – 6.5, p<0.001) for death compared to patients with AKI 1, AKI 2, or no AKI. This was highest in patients with femoral neck fracture (24.6 [8.9 – 67.9, p<0.001]) and pancreatitis (16.1 [2.2 – 119.6, p=0.007]). These were both higher than the OR for death with AKI in any specific medical diagnosis. There were no deaths in patients with appendicitis or ENT diagnoses with any AKI or AKI 3, and there were no deaths in patients with abscesses and AKI 3. For patients with NTICB, both AKI and AKI 3 were associated with a lower risk of death than their respective comparator groups, although in the latter case this did not reach statistical significance. For any AKI, the OR was 0.6 (0.5- 0.8, p=0.003), and AKI 3 was 0.8 (0.2 – 2.9, p=0.737). These results all detailed in Table 3-5.

Table 3-5. Comparative risk for death in medical and surgical admissions with AKI

Diagnosis	Adjusted OR for death			
	AKI 3 versus all others		Any AKI versus no AKI	
	OR	95% CI	OR	95% CI
Medical				
ACS	12.8	4.8 -3 3.8	8.9	5.8 - 13.5
ALD	7.1	3.3 - 14.8	3.0	1.7 - 5.2
CAP	5.7	4.2 - 7.7	3.9	3.4 - 4.6
COPD	11.3	5.1 - 24.4	6.6	4.7 - 9.2
GIB	5.9	2.1 - 16.6	4.2	2.3 - 7.6
HF	6.2	3.5 - 11.0	6.0	4.3 - 8.4
Sepsis	4.2	2.7 - 6.4	3.5	2.6 - 4.6
UTI	5.9	3.7 - 9.2	4.6	3.3 - 6.3
Overall	6.2	5.2 - 7.4	4.7	4.3 - 5.2
Surgical				
Abscess	-	-	1.1	0.1-20.5
Appendix	-	-	-	-
Chole	9.4	3.2 – 27.3	3.4	1.9-6.3
ENT	-	-	-	-
NOF	24.6	8.9 – 67.9	3.8	2.6-5.6
NTICB	0.8	0.2 – 2.9	0.6	0.5-0.8
Panc	16.1	2.2 – 119.6	9.7	2.5-37.4
TICB	1.1	0.1 – 9.0	1.7	1.2-2.5
Overall	4.0	2.4 - 6.5	1.8	1.5-2.1

Table key: OR = odds ratio, 95% CI = 95% confidence interval, p = p value
ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community acquired pneumonia, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, HF – heart failure, sepsis – sepsis (any source), UTI – urinary tract infection. Abscess – abscess (any source), appendix - acute appendicitis, Chole - Cholecystitis/cholangitis, ENT (ear, nose and throat) – ENT (any source), NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed, Panc - acute pancreatitis, TICB - Traumatic Intra Cranial Bleed. *- denotes unable to calculate due to lack of episodes

3.5.4 AKI associated critical care admissions

There were 9001 admissions to critical care, with admission numbers greater in the surgical diagnoses (1852, 20.1%) than the medical diagnoses (606, 6.7%). Admission to critical care in patients with medical diagnoses and any AKI had a OR of 9.6 (95% confidence interval 8.6 – 10.8, p<0.001) in comparison to medical patients without AKI. For individual medical diagnoses, the highest OR for admission to critical care associated with AKI was for heart failure. Here, the adjusted OR was 37.2 (18.9 – 73.4, p<0.001). Overall for medical patients, those with an AKI 3 compared to any of AKI 1, AKI 2 or no AKI had a OR of 3.4 (2.7 – 4.1, p<0.001) for risk of admission to critical care. Patients with ACS had the highest OR at 8.6 (1.9 – 37.2, p=0.004), followed by those with heart failure (7.8 [2.7 – 21.9, p<0.001]). Sepsis was associated with the lowest increased risk for critical care admission in both any AKI (6.8 [5.2 – 9.0, p<0.001]) compared to no AKI, and AKI 3 (2.2 [1.4 – 3.5, p=0.001]) compared to other patients. This most likely reflects the higher baseline rate of adverse outcome in these diagnoses. The event rates for critical care admissions for each diagnosis, in the overall population, as well as those with any AKI and AKI 3, is found in 3-6.

Table 3-6. Comparative risk for critical care admission in medical and surgical admissions with AKI

Diagnosis	Total	All patients		AKI 3		Any AKI N	
		N	%	N	%	N	%
Medical							
ACS	4266	46	1.1	2	4.3	21	45.7
ALD	581	35	6.0	9	25.7	21	60.0
CAP	7232	248	3.4	38	15.3	145	58.5
COPD	4234	27	0.6	3	11.1	15	55.6
GIB	1615	42	2.6	6	14.3	22	52.4
HF	1652	13	0.8	4	30.8	9	69.2
Sepsis	1672	123	7.4	30	24.4	87	70.7
UTI	4800	72	1.5	22	30.6	52	72.2
Overall	26052	606	2.3	114	18.8	372	61.4
Surgical							
Abscess	1352	8	0.6	2	25.0	0	0.0
Appendix	683	40	6.1	0	0.0	10	25.0
Chole	2261	117	5.2	8	6.8	51	43.6
ENT	657	3	0.5	0	0.0	0	0.0
NOF	1815	110	6.1	3	2.7	43	39.1
NTICB	2830	975	34.5	12	1.2	340	34.9
Panc	936	54	5.8	5	9.3	25	46.3
TICB	2026	545	26.9	5	0.9	184	33.8
Overall	12560	1852	14.7	35	1.9	653	35.3

Table key: % AKI = percent of AKI events that were AKI 3, % cases = % of patients with selected diagnosis who had AKI 3 / any AKI.
ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community acquired pneumonia, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, HF – heart failure, sepsis – sepsis (any source), UTI – urinary tract infection. Abscess – abscess (any source), appendix - acute appendicitis, Chole - Cholecystitis/cholangitis, ENT (ear, nose and throat) – ENT (any source), NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed, Panc - acute pancreatitis, TICB - Traumatic Intra Cranial Bleed.

The OR for admission to critical care in any surgical diagnosis for patients with any AKI was 4.3 (3.8 – 4.9, p<0.001) compared to patients without AKI. The surgical diagnosis with the highest OR was appendicitis (6.0, [2.1 – 17.7, p=0.001]), followed by pancreatitis (5.4 [2.8 – 10.6, p<0.001]). The lowest increased risk among surgical diagnoses was in NTICB (2.4 [1.9 – 3.0, p<0.001]) and femoral neck fracture (2.5 [1.6 – 3.8, p<0.001]). Patients with a surgical diagnosis and an AKI 3 had a OR of 2.1 (1.3 – 3.4, p=0.002) for risk of admission to critical care compared to surgical patients with any of AKI 1, AKI 2, or no AKI. Of specific surgical diagnoses, pancreatitis had the highest increased risk in the presence of AKI 3 at 8.1 (1.8 – 35.3, p=0.006). The lowest OR for admission to critical care in the surgical diagnoses with AKI 3 was in patients with a femoral neck fracture (1.3 [0.4 – 5.0, p=0.675]). These comparisons are shown in Table 3-7.

Table 3-7. Comparative risk for critical care admission in medical and surgical admissions with AKI

Diagnosis	Adjusted OR for critical care admission					
	AKI 3 versus all others			Any AKI versus no AKI		
	OR	95% CI	p	OR	95% CI	p
Medical						
ACS	8.6	1.9-37.2	0.004	9.4	6.0-14.9	<0.001
ALD	2.7	1.2-5.9	0.018	12.7	7.3-22.1	<0.001
CAP	3.3	2.2-4.6	<0.001	8.3	6.9-10.0	<0.001
COPD	4.5	1.3-14.8	0.015	13.5	7.9-22.8	<0.001
GIB	3.1	1.2-7.8	0.02	8.2	5.1-13.2	<0.001
HF	7.8	2.7-21.9	<0.001	37.2	18.9-73.4	<0.001
Sepsis	2.2	1.4-3.6	<0.001	6.8	5.2-9.0	<0.001
UTI	3.8	2.4-5.9	<0.001	17.1	12.8-23.0	<0.001
Overall	3.4	2.7-4.1	<0.001	9.6	8.6-10.8	<0.001
Surgical						
Abscess	-	-	-	4.1	0.6-29.0	0.163
Appendix	-	-	-	6.0	2.1-17.7	0.001
Chole	4.5	1.6-11.6	0.002	3.9	2.6-6.1	<0.001
ENT	-	-	-	-	-	-
NOF	1.3	0.4-5.0	0.675	2.5	1.6-3.8	<0.001
NTICB	1.6	0.5-4.9	0.416	2.4	1.9-3.0	<0.001
Panc	8.1	1.8-35.3	0.006	5.4	2.8-10.6	<0.001
TICB	1.6	0.3-8.1	0.529	4.5	3.3-6.1	<0.001
Overall	2.1	1.3-3.4	0.002	4.3	3.8-4.9	<0.001

Table key: OR = odds ratio, 95% CI = 95% confidence interval, p = p value
ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community acquired pneumonia, COPD – chronic obstructive pulmonary disease, GIB – gastro-intestinal bleed, HF – heart failure, sepsis – sepsis (any source), UTI – urinary tract infection. Abscess – abscess (any source), appendix - acute appendicitis, Chole - Cholecystitis/cholangitis, ENT (ear, nose and throat) – ENT (any source), NOF - Fractured (neck of femur) NOF, NTICB- Non-Traumatic Intra Cranial Bleed, Panc - acute pancreatitis, TICB - Traumatic Intra Cranial Bleed.

3.6 Discussion

The presented data provide granularity to, and add to our current understanding of, the epidemiology and associated risks of AKI in specific medical and surgical inpatient populations.

3.6.1 AKI incidence

The incidence of any AKI and AKI 3 was highest in sepsis, reflecting the known complication of sepsis and haemodynamic compromise. In sepsis management it needs to be emphasized that almost one third of patients will suffer an AKI, and that fluid optimization, source control, a careful approach to use of nephrotoxic medication, and regular ongoing review are important. [14,15]

Overall, there were smaller numbers of patients suffering any stage of AKI in the surgical population. The majority were confined to 2 diagnoses: femoral neck fracture and non-traumatic intracranial bleed. Very few surgical patients were found to suffer AKI 3, which is likely due to a combination of confounding issues. The ICD-10 coded diagnoses are discharge diagnoses and patients may be too unwell to be investigated for, or to have their management changed by, a surgical diagnosis. This may not therefore be their primary coded discharge diagnosis. In most NHS hospital models, surgical patients are pre-selected by the surgical team and are composed of more medically fit patients who are suitable for anaesthetic.[16] This consequently leaves those with greater age and comorbid burden who would be destined for conservative management of a potentially surgical problem under the care of the medical teams.

An improved understanding of the incidence and risk of AKI and related outcomes in relation to the specific underlying condition could support the design of bespoke teaching packages and facilitate targeting of resources. It could direct education to areas or teams that deal with higher numbers of AKI and AKI 3 to maximize effectiveness of AKI prevention and overall patient care. The scarcity of AKI events in patients with abscesses, appendicitis, pancreatitis or ENT diagnoses also argues in support of early and regular medical or renal input, as expertise is unlikely to be maintained in those fields. This supports an argument not just for personalised care for patients but also personalised education for their doctors.

3.6.2 AKI associated mortality

The high likelihood of death in community-acquired pneumonia and alcoholic liver disease reflects the overall physiological condition of patients with these diagnoses. These two diagnoses are suggestive of progressive single organ failure and are associated with significant mortality with or without sepsis, and with or without AKI.[17]

Most significantly for the surgical specialties and the orthogeriatrics team, not only were patients with a femoral neck fracture the most likely to get an AKI, but their likelihood of death was also highest, with the lowest chance for critical care admission. Again, this likely reflects the underlying frailty of the patient, irrespective of chronological age and the severity of the intercurrent illness causing AKI. However, it highlights important discrepancies in management of different surgical patients and deserves further research to understand any inequalities in care (e.g. access of aged patients to higher level care).

The majority of admissions for patients with coded diagnoses of ACS and COPD are short stays with mild exacerbations of disease. Therefore, if these patients have a significant additional pathology or haemodynamic disturbance that leads to an intercurrent AKI, then this would plausibly be linked to a higher risk of death.

3.6.3 AKI associated critical care admissions

Admissions to critical care are positively skewed towards surgical patients. Surgical patients have a low threshold for pre-emptive critical care admission compared to medical diagnoses. The Royal College of Surgeons criteria states that if patients have a >10% chance of mortality post-operatively they should be cared for in a critical care facility.[18] This may also contribute to the reduced OR for death seen in surgical patients who suffer AKI in comparison to medical patients suffering an AKI. This could lend support to recommend therefore that medical patients with the highest risk of death should also be transferred early to critical care.

The level of granularity provided here could be used to model an inpatient journey or ‘forecast’ predictable care needs. It provides weight and data regarding level of care likely to be required for different specialty components of the hospital population, geographical location for this need, and specialty team input required. Feasibly, this

could be used as a trigger threshold for acute medical review or renal input into surgical specialties in a timely manner, or as a regular occurrence built into job plans. It could aid planning during winter pressures for elective procedures depending on likely critical care bed availability or projected occupancy. The data could also lend support for provision of palliation or bereavement provision and advice both in and out of hours.

3.7 Limitations

Salford Royal NHS Foundation Trust has a long history of digital excellence and has won awards for digital maturity. However, the ICD 10 codes and coding practice are prone to incompleteness or redundancy when linked to primary care. This may affect the categories of diagnosis and count of comorbidities.

There is an inherent selection bias for patients undergoing surgery or selected to be under surgical care. If a patient with multiple co-morbidities were to be considered for conservative management of a surgical pathology, the medical team may look after the patient.

Critical care covers a 24-bedded unit for general patients, a neurosurgical unit (8 beds) and a surgical high-dependency unit (8 beds). In addition to its critical care services, the Trust has a medical high care unit that has 8 beds and provides high-flow oxygen, non-invasive ventilation and cardiac monitoring. This model often supports patients unsuitable for escalation to critical care but who still are categorised as critical care in terms of coding. Therefore, the data for medical admissions to critical care may be slightly overestimated in comparison to similar tertiary teaching hospitals that lack similar units.

3.8 Conclusion

Increasingly, AKI should be considered ‘an illness barometer’ that affects the outcome of any underlying condition. The kidneys can be seen as sentinel organs: their dysfunction is a marker of the unwell patient. In conjunction with clinical acumen, an AKI alert in combination with an early warning score could be an indication for early daily senior medical input. The quantitative data provided here

can also support managerial decisions in terms of bed management - for example, with an AKI defining patients who should not be outlied (placed outside an acute medical ward).

The clinical impact of AKI differs across medical and surgical diagnoses, but is a significant contributor to the risk for death and critical care admission. This body of work may indicate a benefit to a more diagnosis-specific stratified approach to personalised AKI care after acute admission in respect of decisions for investigations and management, escalation of care, prompt referral or palliation.

Compliance with ethical standards

The authors have no conflicts of interest to declare.

There was no funding support associated with the creation of this manuscript.

Data for all non-elective inpatient episodes at Salford Royal between 1st March 2011 and 31st December 2017 were extracted anonymously from the Trust 'data warehouse'. No patient identifiable information were extracted as part of the dataset. Salford Royal is a global digital exemplar site and data extra extraction relating to patient episodes could be performed with complete anonymization and with a high level of granularity for event data. Data extraction was performed as part of an AKI quality improvement initiative. This was exempt from specific ethical approval as it was anonymised data, but anonymyzation and data extraction occurred in accordance with local information governance policy.

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Chapter 4

The effect of AKI stage on mortality in different admission diagnoses; is AKI 2 comparable to AKI 3?

4.1 Rationale

This chapter explores the relationship between severity of acute kidney injury (AKI), mortality and reason for admission to hospital. In the previous chapter we have seen that AKI 3 in particular conveys a high risk of mortality. However based on observational experience in clinical practice as a medical registrar often patients I encountered were more unwell with AKI 2 than AKI 3, or significantly vice versa, depending on their other presenting features. Many previous studies have used AKI 2 or 3 as a combined end point, on the basis that outcomes are sufficiently poor with AKI 2 that it can be considered alongside AKI 3. However, this is poorly described in the literature. In particular, it is not clear whether the relative impact of AKI 2 and AKI 3 differs between individual presenting diagnoses.

4.2 Abstract

Introduction

AKI is common and associated with significant mortality. The relative impact of AKI 2 and AKI 3 on inpatient mortality is not well known, and current literature often describes heterogeneous groups, largely in the consequence of the low numbers of patients available for study. In this chapter we determine the extent to which AKI 2 confers risk of death compared to AKI 3 in individual presenting diagnoses.

Methods

Data were extracted anonymously from the Trust 'data warehouse' for admissions between 2011and 2017. We applied KDIGO AKI criteria to establish AKI stage. Ten

common ICD-10 coded admission diagnoses with high prevalence of AKI were chosen. Odds ratios (OR) for death were calculated for patients with each AKI stage (compared to admissions without AKI). Analyses were performed using binary logistic regression, adjusted for age, pre-existing chronic kidney disease, co-morbid index, and gender.

Results

There were 30,697 patient episodes among the selected diagnoses, with 4,673 AKI episodes. The proportion of patients dying with an AKI increased with AKI stage: from 6.9% in those without AKI; to 19.3% in AKI stage 1; 31.7% in AKI stage 2; and 42.3% in AKI stage 3. The OR for death in AKI 3 versus no AKI was highest in patients admitted with fractured neck of femur (OR 40.9 [14.0-119.3], p = <0.001)), followed by patients admitted with acute coronary syndrome (OR 20.8 [8.0-54.2], p = <0.001). AKI 3 was associated with death in approximately half of cases for patients with heart failure, community-acquired pneumonia, alcoholic liver disease, sepsis and fractured neck of femur. Only three admission diagnoses had statistically significant increases in OR for death in AKI 3 compared to AKI 2 (community acquired pneumonia; fractured neck of femur; urinary tract infection).

Conclusion

This study demonstrates that there is significant risk of death associated with escalating AKI stage. However this differs by admission diagnosis. AKI stage 2 has a similar risk for death as AKI stage 3 in several diagnoses. Both the cause and effect of AKI are heterogeneous, and studies should not be so reductive as to take a binary view of patients either having AKI or not: in particular, consideration of the spectrum of AKI severity should be separated from consideration of AKI's interaction with different disease processes to examine risk and plan tailored management strategies.

4.3 Introduction

Acute kidney injury (AKI) is a common syndrome with a spectrum of severity. It is involved in up to one in five emergency patient admissions to hospital in the UK.[1] To date, research has proven that AKI has a wide range of causes and this heterogeneity has lead to difficulties in understanding not only the risk for AKI, but also the effects of AKI in both the community and hospital populations.

AKI is classified according to severity using the KDIGO classification system.[2] Milder deteriorations in renal function are classified as AKI stage 1 and moderate cases as AKI stage 2. The most severe cases, including those that feature acute need for dialysis, are classified as AKI stage 3. Due to the relative infrequencies of AKI stage 2 and 3, these are often considered together in studies. However, the literature is fairly divided on whether this is an appropriate strategy, given the heterogeneity of causes for any AKI, and the possibility that outcomes will differ significantly between these two stages. Greater granularity of outcomes within the different stages of AKI may lead to greater understanding of their individual clinical impacts, and whether it is appropriate to combine these as a single outcome in studies.

Several international studies show that mortality varies greatly with AKI from 11.6% to 70.0% in a variety of settings encompassing both intensive care and general hospital inpatients.[3,4] Studies often dichotomise mortality and outcomes into AKI or patients without AKI.[5] The FINNAKI trial showed initial rates of mortality were similar in AKI stage 2 and 3 in the first few days of ICU admissions.[6] However, there was consensus among several studies that there is an increase in mortality in AKI 2 and AKI 3 in comparison to AKI 1. [7–9]

Other studies have shown that long-term mortality outcomes are similar in lower stages of AKI [10], which may suggest that those who survive the initial insult in AKI stage 2 will have comparable outcomes to those with AKI stage 1. This may also point to differences in baseline creatinine and AKI recovery, which are significant contributors to future morbidity and mortality but beyond the scope of this work.

When patients suffer AKI 2 and AKI 3 it is often considered to be more serious. This study considers not only the extent to which the AKI stage has an effect on mortality between AKI 2 and AKI 3, but also whether the admission diagnoses in these patients may also have a bearing on the impact of different stages of AKI. The emerging data surrounding ‘organ cross talk’ supports the theory that AKI would have stronger associations with mortality in certain diagnoses. Previous studies with smaller data sets have been unable to meaningfully demonstrate the difference in effect between AKI 2 and AKI 3 in different admission settings and their effect on mortality. This study looks at mortality associated with AKI at any stage and also the relative risk of AKI stage 3 over AKI stage 2 in different clinical admissions.

4.4 Methods

4.4.1 Setting

The population and demographics of Salford are described in the generic methods chapter.

4.4.2 Data

Data for all non-elective patient admissions to Salford Royal NHS Foundation Trust between 1st March 2011 and 31st of December 2017 was extracted from the Trust 'data warehouse'. As a global digital exemplar site it is possible to extract the data relating to patient episode with complete anonymisation and a high level of granularity.

Data was extracted for age, gender, ICD-10 coded admission diagnosis, comorbidities, inpatient mortality, laboratory creatinine values and AKI stage. Ten of the most common admission diagnoses with high AKI incidence were selected based on ICD 10 codes determined at discharge. These are shown in Table 4-1. Patients often have more than one diagnosis during admission. However, patients were grouped according to their primary coded diagnosis for the purposes of the study.

The Trust central pathology laboratory provides biochemistry services for all inpatient and outpatient venous samples, including those from primary care. From March 2011 until January 2015, a compensated kinetic Jaffe method with an inter-assay coefficient of variance of 1.7% at 193umol/L (Roche Cobas 8000) was used to measure all serum creatinine values (normal creatinine range, male: 62-106 μmol/L; female: 44-80 μmol/L). From January 2015 to December 2017 the method was a compensated kinetic Jaffe method with an inter-assay coefficient of variance of 2.9% at 156 μmol/L (Siemens, Advia) (normal creatinine range, male: 62-115 μmol/L; female: 44-97 μmol/L). The Kidney Disease Improving Global Outcomes (KDIGO) AKI 'creatinine based' criteria were manually applied retrospectively using the National AKI algorithm to establish AKI stage.[11,12] There were no urine output data available to include in this analysis.[13]

Table 4-1 The 10 most common diagnosis categories and their relative frequency amongst all admissions

Key	Diagnosis	Frequency (%)	Key	Diagnosis	Frequency (%)
ACS	Acute coronary syndrome	4266 (2.2)	**HF**	Heart failure	1652 (0.8)
ALD	Alcoholic liver disease	582 (0.3)	**NOF**	Femoral neck fracture (NOF)	1815 (0.9)
CAP	Community-acquired pneumonia	7232 (3.7)	**NTICB**	Non Traumatic Intra Cranial Bleed	2830 (1.4)
COPD	Chronic obstructive pulmonary disease	4234 (2.1)	**Sepsis**	Sepsis (any source)	1672 (0.8)
GIB	Gastro-intestinal bleed	1615 (0.8)	**UTI**	Urinary tract infection	4800 (2.4)

4.4.3 Statistical analysis

Patient characteristics were compared for each selected admission diagnosis. Odds ratios (OR) were calculated for inpatient death after AKI onset in patients with each of the different stages of AKI compared to patients without AKI. The analysis was then repeated for AKI stage 3 compared to AKI stage 2. All of the analyses were performed using logistic regression, adjusted for age, pre-existing chronic kidney disease (CKD), co-morbidity index, and gender. IBM's Statistical Package for the Social Sciences (SPSS) version 23 for Mac [SPSS (UK) Ltd, Woking, Surrey, UK] was used for analyses.

4.5 Results

4.5.1 Demographics

There were 197,884 non-elective patient admission episodes available for analysis over 80 months from March 2011 to December 2017, shown in Table 4-2. Within the 10 selected admission diagnoses there were 30,697 patient episodes. There was a more even split in gender between the selected diagnoses (47% male), that the overall population (43% male). There was a high proportion of chronic kidney

disease (11.5%) compared to the overall population (8.7%). There was a high mean comorbidity burden (9.5 [1-17] versus 6.9[1-17]) and the mean age was greater in the selected diagnoses in comparison to the overall population (69.6 years [SD 22.3] versus 55.5 years [SD 16.9]).

Within the selected diagnoses, there were 4,673 episodes of AKI. The proportion of patients suffering an AKI was higher in the selected diagnoses than the overall population, but the proportion of patients suffering an AKI 3 was lower (2.2% versus 2.9%). There was a significantly higher proportion of death in the selected diagnoses (9.7%) than in the overall population (3.4%).

Table 4-2 Overall population demographics and specific breakdown of medical and surgical selected diagnoses (adapted from Sykes et al. PLOS ONE[13])

Demographic	Overall	Selected diagnoses
Patients	197,884	30,697 (15.5%)
Male gender (%)	85,090 (43%)	14,423 (47%)
Age mean (SD)	55.5 (22.3)	69.6 (16.9)
CKD (%)	17,262 (8.7%)	3,541 (11.5%)
Comorbidities (range)	6.9 (1-17)	9.5 (1-17)
No AKI (%)	182,667 (92.3%)	26,024 (84.8%)
Any AKI (%)	15,217 (7.7%)	4673 (15.2%)
AKI 1 (%)	9478 (4.8%)	2946 (9.6%)
AKI 2 (%)	3185 (1.6%)	1049 (3.4%)
AKI 3 (%)	5740 (2.9%)	678 (2.2%)
Death (%)	6749 (3.4%)	2981 (9.7%)

4.5.2 Mortality

There were 2,981 deaths amongst the 30,697 patients within the selected common diagnoses (9.7%), as shown in Table 4-3. The proportion of deaths increases significantly with AKI stage. During admission 6.9% of patients without AKI died, whereas 19.3% of patients with AKI 1 died, as did 31.7% of patients with AKI 2 and 42.3% of patients with AKI 3.

Patients with non-traumatic intracranial bleeds were the group most likely to die without AKI (21.4%) in comparison to their likelihood of death if they are suffering any stage of AKI. A larger proportion of patients with sepsis (11.5%) and

community acquired pneumonia (11.4%) died without AKI in comparison to all the other medical admission diagnoses.

In more severe stages of AKI the data showed that there were similar proportions of deaths in patients with AKI 2 and AKI 3 for the diagnoses of heart failure (50.0% and 47.4% respectively) and acute coronary syndrome (36.5%, 33.3%).

For a number of diagnoses, mortality approached or exceeded 50% where an AKI 3 was present. The proportion of patients admitted with heart failure dying with AKI 3 in comparison to no AKI was 47.4% versus 11.8%; for those admitted with community-acquired pneumonia it was 52.7% versus 16.0%; for COPD 50.0% versus 4.6%; for alcoholic liver disease 52.8% versus 12.7%; for sepsis 45.7% versus 18.2%; and for fractured neck of femur 54.5% versus 6.9%.

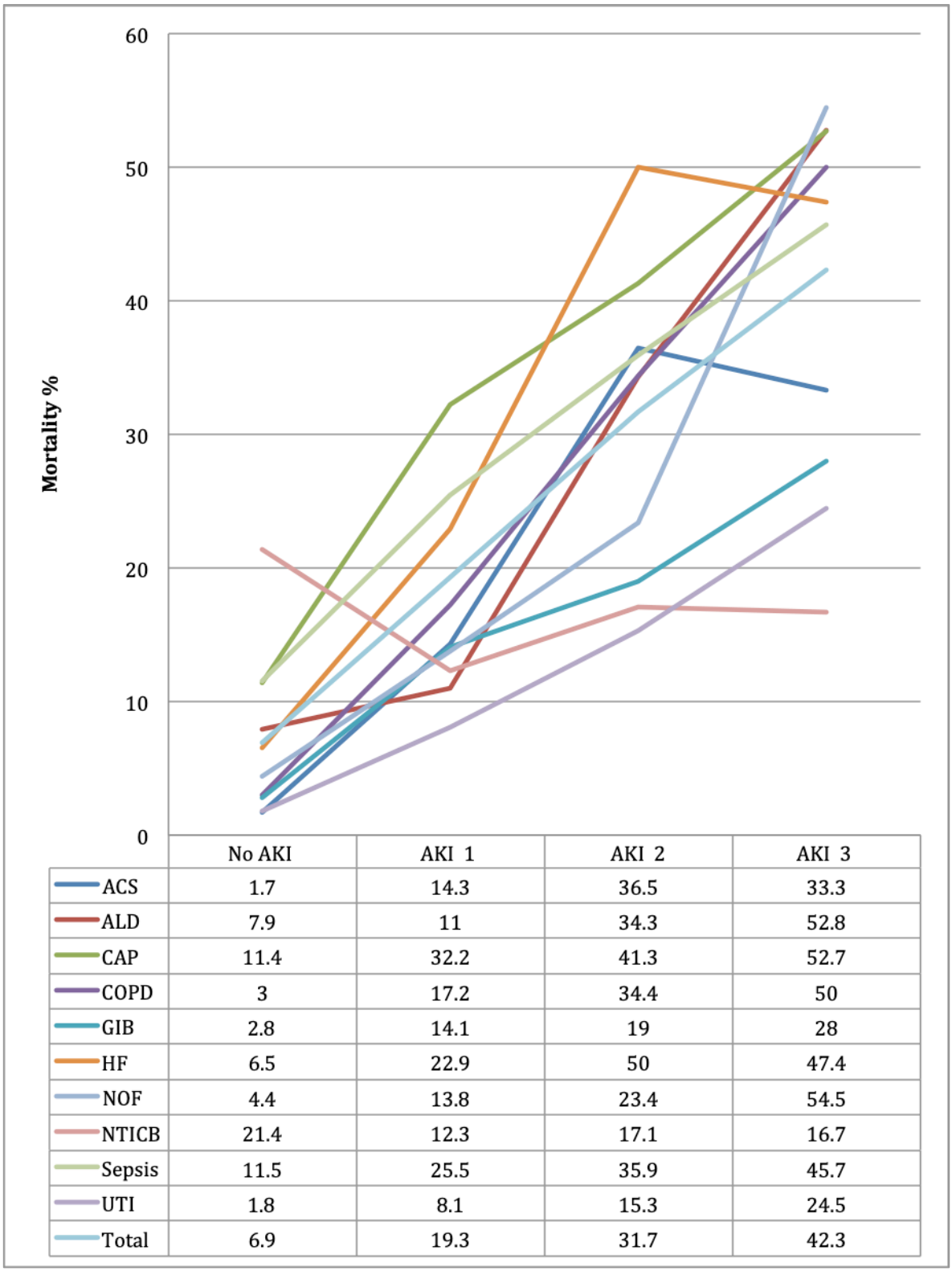
These different rates are clearly shown in Figure 4-1. Most striking is the non-traumatic intracranial bleed rate that appears fairly static across all patients with or without AKI. It is also clear that for the majority of other diagnoses the percentage of patients dying with AKI increases as AKI stage increases. The two notable exceptions in diagnoses are patients with acute coronary syndrome or heart failure. These two groups show an increase in mortality from no AKI up to AKI stage 2, and then both show a decrease in mortality for AKI stage 3.

Table 4-3 Count of patients and mortality by AKI stage

	No AKI (n)	No AKI death (n)	No AKI death (%)	AKI 1 (n)	AKI 1 death (n)	AKI 1 death (%)	AKI 2 (n)	AKI 2 death (n)	AKI 2 death (%)	AKI 3 (n)	AKI 3 death (n)	AKI 3 death (%)	Total (n)	Total death (n)	Total death (%)
ACS	4011	69	1.7	168	24	14.3	63	23	36.5	24	8	33.3	4266	124	2.9
ALD	428	34	7.9	82	9	11.0	35	12	34.3	36	19	52.8	581	74	12.7
CAP	5979	683	11.4	738	238	32.2	312	129	41.3	203	107	52.7	7232	1157	16.0
COPD	3910	118	3.0	233	40	17.2	61	21	34.4	30	15	50.0	4234	194	4.6
GIB	1463	41	2.8	85	12	14.1	42	8	19.0	25	7	28.0	1615	68	4.2
HF	1306	85	6.5	227	52	22.9	62	31	50.0	57	27	47.4	1652	195	11.8
NOF	1483	65	4.4	246	34	13.8	64	15	23.4	22	12	54.5	1815	126	6.9
NTICB	2312	495	21.4	424	52	12.3	76	13	17.1	18	3	16.7	2830	563	19.9
Sepsis	1140	131	11.5	271	69	25.5	145	52	35.9	116	53	45.7	1672	305	18.2
UTI	3992	72	1.8	472	38	8.1	189	29	15.3	147	36	24.5	4800	175	3.6
Total	26024	1793	6.9	2946	568	19.3	1049	333	31.7	678	287	42.3	30697	2981	9.7

Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3. OR – Odds ratio, p – p value (n) = number of patients.

Figure 4-1 Comparison of the percentage of mortality by AKI stage in the different diagnoses



	No AKI	AKI 1	AKI 2	AKI 3
ACS	1.7	14.3	36.5	33.3
ALD	7.9	11	34.3	52.8
CAP	11.4	32.2	41.3	52.7
COPD	3	17.2	34.4	50
GIB	2.8	14.1	19	28
HF	6.5	22.9	50	47.4
NOF	4.4	13.8	23.4	54.5
NTICB	21.4	12.3	17.1	16.7
Sepsis	11.5	25.5	35.9	45.7
UTI	1.8	8.1	15.3	24.5
Total	6.9	19.3	31.7	42.3

Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial

Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3

4.5.3 Risk of mortality in AKI stage in comparison to patients without AKI

Overall, there was an odds ratio (OR) of 2.6 (2.3-2.8, p = <0.001) of mortality in patients with AKI 1 in comparison to patients without AKI (table 4-4). The highest relative risk among the admission diagnoses was seen in patients with ACS (OR = 5.1 [3.0-8.7], p = <0.001) and COPD (OR = 4.7 [3.1-7.0], p = <0.001), and the lowest relative risk was seen in non-traumatic intracranial bleeds (OR = 0.6 [0.4-0.8], p = 0.003) and sepsis (OR = 2.3 [1.7-3.3], p = <0.001).

For patients with AKI 2, overall there was an OR of 4.9 (4.2-5.6, p = <0.001) of mortality in comparison to patients without AKI. The highest relative risk was again in patients with ACS (OR = 17.6 [9.6-32.5], p = <0.001), with heart failure showing a similarly increased relative risk (OR = 13.1 [7.4-23.2], p = <0.001). The lowest relative risks were alcoholic liver disease and gastrointestinal bleeds (both OR = 3.9 [1.7-8.9], p = <0.001), and sepsis (OR = 4.2 [2.8-6.3], p = <0.001).

Overall, the relative risk of mortality in AKI 3 in comparison to no AKI was 8.2 (7.0-9.7, p = <0.001). In patients admitted with fractured neck of femur there was a significant risk of mortality (OR = 40.9 [14.0-119.3], p = <0.001) in comparison to patients without AKI. The next highest relative risk was seen in patients with ACS (OR = 20.8 [8.0-54.2], p = <0.001) and COPD (OR = 17.7 [8.0-39.1], p = <0.001), with the lowest relative risk was in sepsis (OR = 6.3 [4.0-10.0], p = <0.001) and gastrointestinal bleeds (OR = 7.9 [2.7-23.6], p = <0.001)**.**

The only diagnosis where mortality was lower in patients with AKI than without was intra-cranial bleeding. Here, the relative risk of death with each stage of AKI was broadly similar (OR = 0.6 [0.4-0.8], p =0.003 for AKI 1 compared to no AKI; OR = 0.8 [0.4-1.5], p = 0.498 for AKI 2; OR = 0.7 [0.2-2.5], p = 0.572 for AKI 3.

The most common pattern of evolving relative risk with increasing AKI stage was seen in sepsis, UTI, pneumonia, and ALD, in all of which there was a progressive and largely linear increase in risk of death with increasing severity of AKI. COPD also followed this pattern but with a much higher overall risk than the preceding four diagnoses. (Figure 4-2).

Fractured neck of femur also demonstrated an increasing relative risk with each stage of AKI, but the added risk in AKI 3 was notably different. Here, the OR was 5.3 (2.7-10.5, p = <0.001) in AKI 2 compared to no AKI, but for AKI 3 was 40.9 (14.0-119.3, p = <0.001).

Gastrointestinal bleeding followed a different pattern: AKI 1 and 2 shared a similar relative risk compared to no AKI (AKI 1 OR = 3.5 [1.6-7.5], p = <0.001; AKI 2 OR = 3.9 [1.5-10.0], p = 0.006). The relative risk of death in AKI 3 was much higher than these (OR = 7.9 (2.7-23.6), p = <0.001).

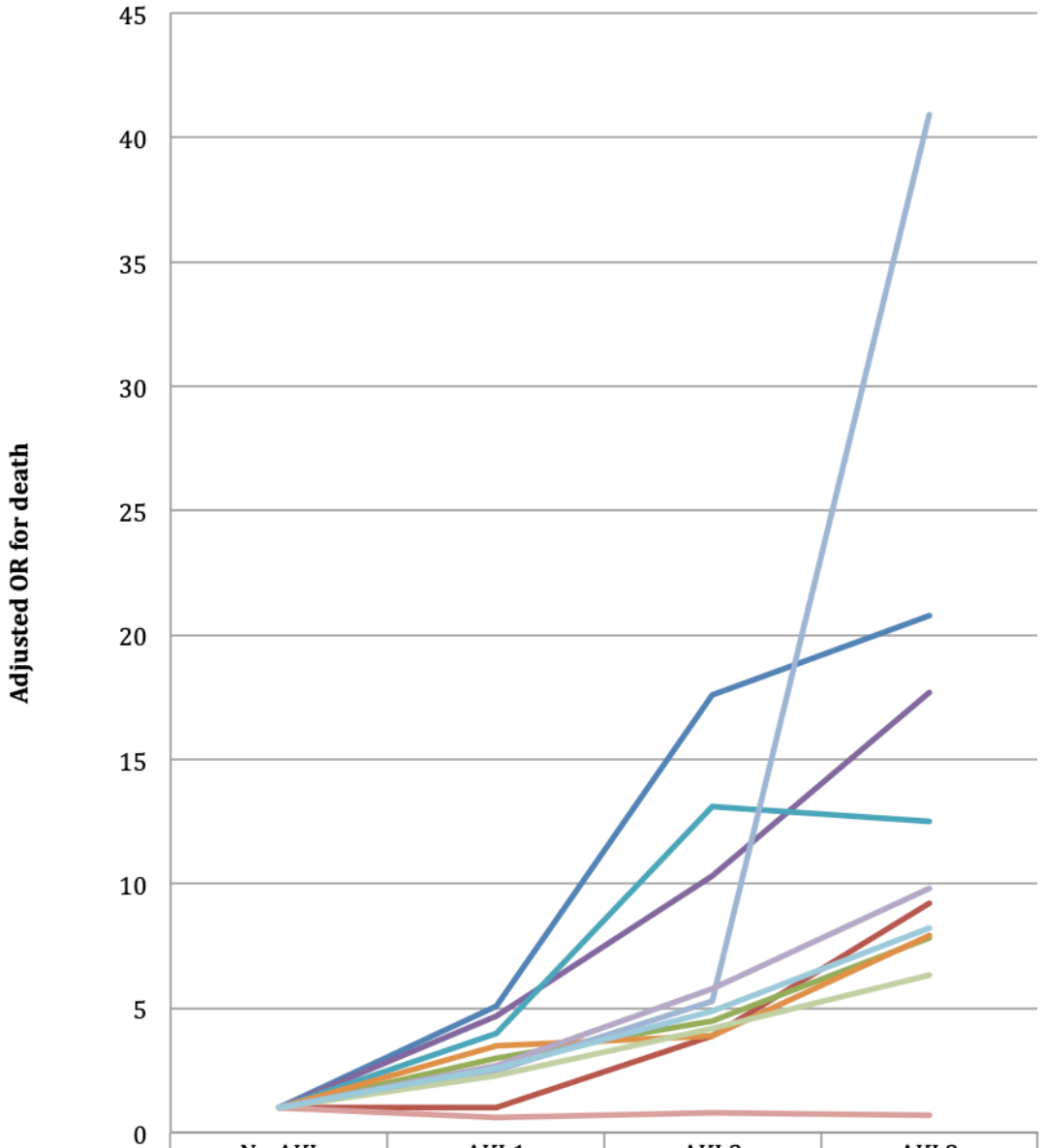
The two cardiovascular diagnoses (ACS and heart failure) followed a different pattern still. Here, the increasing relative risk of death with increasing AKI stage was higher than with most other diagnoses. However, that increased relative risk manifested most clearly between AKI 1 and AKI 2, with little relative increase in relative risk between AKI 2 and AKI 3 (Figure 4-2).

Table 4-4 Adjusted risk of mortality by AKI stage in selected diagnoses in comparison to no AKI / AKI stage 0

	AKI stage					
	1		2		3	
	OR	p	OR	p	OR	p
ACS	5.1 (3.0-8.7)	<0.001	17.6 (9.6-32.5)	<0.001	20.8 (8.0-54.2)	<0.001
ALD	1.0 (0.4-2.3)	0.981	3.9 (1.7-8.9)	<0.001	9.2 (4.1-10.6)	<0.001
CAP	3.0 (2.5-3.6)	<0.001	4.5 (3.4-5.7)	<0.001	7.8 (5.7010.7)	<0.001
COPD	4.7 (3.1-7.0)	<0.001	10.3 (5.6-18.7)	<0.001	17.7 (8.0-39.1)	<0.001
HF	4.0 (2.7-5.9)	<0.001	13.1 (7.4-23.2)	<0.001	12.5 (6.8-23.0)	<0.001
GIB	3.5 (1.6-7.5)	<0.001	3.9 (1.5-10.0)	0.006	7.9 (2.7-23.6)	<0.001
NOF	2.5 (1.6-3.9)	<0.001	5.3 (2.7-10.5)	<0.001	40.9 (14.0-119.3)	<0.001
NTICB	0.6 (0.4-0.8)	0.003	0.8 (0.4-1.5)	0.498	0.7 (0.2-2.5)	0.572
Sepsis	2.3 (1.7-3.3)	<0.001	4.2 (2.8-6.3)	<0.001	6.3 (4.0-10.0)	<0.001
UTI	2.7 (1.8-4.1)	<0.001	5.8 (3.6-9.5)	<0.001	9.8 (6.0-16.0)	<0.001
Overall	2.6 (2.3-2.8)	<0.001	4.9 (4.2-5.6)	<0.001	8.2 (7.0-9.7)	<0.001

Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3.

Figure 4-2 Comparison of the pattern of increasing risk of death with increasing AKI stages between different diagnoses.



	No AKI	AKI 1	AKI 2	AKI 3
ACS	1	5.1	17.6	20.8
ALD	1	1	3.9	9.2
CAP	1	3	4.5	7.8
COPD	1	4.7	10.3	17.7
HF	1	4	13.1	12.5
GIB	1	3.5	3.9	7.9
NOF	1	2.5	5.3	40.9
NTICB	1	0.6	0.8	0.7
Sepsis	1	2.3	4.2	6.3
UTI	1	2.7	5.8	9.8
Overall	1	2.6	4.9	8.2

Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3

4.5.4 AKI 2 versus AKI 3

This section contains a narrative description of the data. The demographics of patients with AKI stages 2 and 3 were different to the general in-patient population and patients with AKI 1. There was a higher prevalence of CKD: 13% compared to 11.5% in the selected diagnoses and 8.5% in the overall hospital population. There was also a higher mean number of comorbidities: 12.9 (SD = 1-17) comorbidities compared to 9.5 (1-17) in the selected diagnoses and 6.5 (1-17) in the overall hospital population. The mean age of patients with an AKI 2 or 3 was 72.7 years (SD = 14.9), compared to 69.6 years (SD = 16.9) in the selected diagnoses with AKI 1 or no AKI and 55.5 years (SD = 22.3) in the overall hospital population.

Overall patients with AKI 3 in comparison to AKI 2 had an excess risk of mortality of OR 1.7 (1.4-21.1, p = <0.001) as shown in Table 4-5. Only three of the individual diagnoses showed this greater risk at a significant p-value, however. The only patients where mortality in AKI 3 was statistically worse than AKI 2 were those admitted with community-acquired pneumonia (OR = 1.8 [1.2-2.6], p = 0.002), urinary tract infections (OR = 2.1 [1.2-3.7, p = 0.015) and fractured necks of femurs (OR 5.0 [1.3-19.3], p = 0.02). AKI 3 was statistically and numerically no worse in terms of mortality compared to AKI 2 for three diagnoses. These were heart failure (OR = 0.8 [0.4-1.8], p = 0.701), ACS (OR = 1.3 [0.4-4.0], p = 0.624), and NTICB (OR = 0.6 [0.1-3.1], p = 0.565).

Table 4-5 Risk of mortality in selected diagnoses in AKI stage 3 in comparison to AKI stage 2

	AKI 3 compared to AKI 2	
	OR	**p**
ACS	1.3 (0.4-4.0)	0.624
ALD	2.1 (0.8-5.6)	0.142
CAP	1.8 (1.2-2.6)	0.002
COPD	2.4 (0.9-6.8)	0.093
GIB	2.8 (0.7-11.4)	0.159
HF	0.8 (0.4-1.8)	0.701
NOF	5.0 (1.3-19.3)	0.02
NTICB	0.6 (0.1-3.1)	0.565
Sepsis	1.7 (1.0-3.0)	0.061
UTI	2.1 (1.2-3.7)	0.015
Overall	1.7 (1.4-21.1)	p<0.001

Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3. OR – Odds ratio, p – p value.

A comparison of patient phenotype in the different AKI stages within each diagnosis is seen in Table 4-6. Overall, patients with any AKI were older (AKI 1 - 72.3 ± 15.4, AKI 2 - 73.5 ± 14.6, AKI 3 - 71.4± 15.3) than those without AKI (69.2 ± 17.2). The proportion of patients with CKD was similar in patients without AKI (11.4%), AKI 1 (11.6%) and AKI 2 (11.3%), but there was a higher proportion of cases of CKD found in patients who suffered an AKI 3 (15.6%). The number of comorbidities increased with AKI stage. Patients without AKI had a mean comorbid burden of 9.1 (±4.0), AKI 1 11.8 (±3.8), AKI 2 12.4 (±3.5) and AKI 3 13.5 (±2.9).

The different patient phenotypes are also shown split by diagnosis in Figures 4-3, 4-4 and 4-5. Figure 4-3 shows the different mean ages of patients by AKI stage and by admission diagnosis. Age appears more closely correlated with admission diagnosis

than with AKI stage. Several of the diagnoses categories demonstrate little variation in age. Moreover age little affected whether patients suffered AKI or not, nor the severity in cases where AKI was present. Patients with alcoholic liver disease were a significantly younger population than the majority of other groups, regardless of AKI stage. Patients with alcoholic liver disease and no AKI had a mean age of 51.2 years (± 11.5) and this varied little among the AKI stages.

Patients with non-traumatic intracranial bleeds and gastrointestinal bleeds were the next youngest groups with the majority of patients in their late fifties and sixties throughout the AKI stages. Patients with all other diagnoses had a mean age in their seventies across the AKI stages.

The percentage of CKD across the diagnoses is shown in Figure 4-4. Overall there is a general increase in percentage of CKD in those who suffer AKI 3. However, patients who were admitted with heart failure were less likely to have CKD as their AKI stage increased. Patients admitted with heart failure without AKI had a 27.3% incidence of CKD; AKI 1 had 19.8%; AKI 2 had 19.4%; and AKI 3 had 10.5%.

There was a significant increase in the rate of CKD seen in patients with a fractured neck of femur and AKI 3, from 8.9% without AKI to 31.8% with AKI 3.

There were low proportions of patients with CKD in those admitted with alcoholic liver disease (0.9-9.8%) or with non-traumatic intracranial bleeds (0-11.1%).

All diagnoses saw an increase in the mean number of comorbidities as AKI occurred or its severity increased.

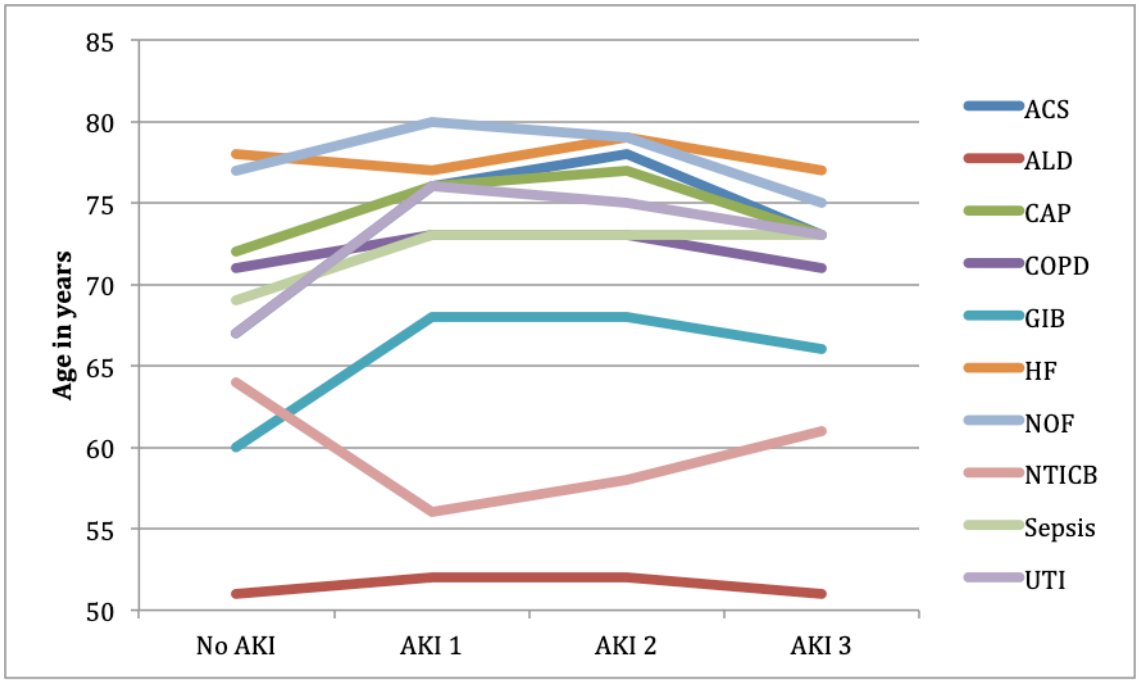
Table 4-6 Comparison of patient phenotype in different AKI stage by diagnosis

Diagnosis	Characteristic	No AKI	AKI 1	AKI 2	AKI 3
ACS	Age (years)	67.4 ± 13.8	76.0 ±12.2	77.7 ± 10.7	73.3 ± 13.3
	CKD (%)	11.1	13.7	11.1	20.8
	Co-morbid (n)	9.1 ± 3.8	12.6 ± 3.3	12.9 ±3.3	12.9 ± 3.6
ALD	Age (years)	51.2 ± 11.5	51.8 ± 10.3	51.6 ± 10.7	51.3 ± 11.0
	CKD (%)	0.9	9.8	2.9	8.3
	Co-morbid (n)	9.4 ± 3.7	11.8 ± 3.9	12.4 ± 2.9	13.2 ± 3.5
CAP	Age (years)	72.1 ± 16.7	75.9 ± 14.0	76.9 ± 12.6	73.1 ± 15.6
	CKD (%)	12.3	12.6	13.1	12.3
	Co-morbid (n)	9.6 ± 4.0	12.1 ± 3.6	12.2 ± 3.4	13.1 ± 3.1
COPD	Age (years)	71.0 ± 11.0	73.4 ± 9.8	72.9 ± 11.5	71.0 ± 10.1
	CKD (%)	8.7	13.3	13.1	10.0
	Co-morbid (n)	8.2 ± 3.6	10.8 ± 3.7	11.8 ± 3.9	14.1 ± 2.6
GIB	Age (years)	60.0 ± 21.2	67.9 ± 16.3	67.5 ± 19.0	65.5 ± 16.8
	CKD (%)	8.3	11.8	9.5	16.0
	Co-morbid (n)	8.1 ± 3.7	11.5 ± 3.6	12.2 ± 4.1	13.3 ± 2.4
HF	Age (years)	78.1 ± 10.9	76.5 ± 10.7	78.5 ± 12.6	77.0 ± 11.3
	CKD (%)	27.3	19.8	19.4	10.5
	Co-morbid (n)	11.2 ± 3.5	13.0 ± 3.3	13.2 ± 3.2	13.9 ± 2.5
NOF	Age (years)	77.2 ± 15.3	80.2 ± 10.9	78.8 ± 12.5	75.0 ± 11.7
	CKD (%)	8.9	8.9	10.9	31.8
	Co-morbid (n)	11.4 ± 4.1	13.5 ± 3.6	14.0 ± 3.3	13.6 ± 4.2
NTICB	Age (years)	64.3 ± 17.0	56.8 ± 13.8	58.3 ± 13.9	61.1 ± 17.3
	CKD (%)	3.7	0.7	0.0	11.1
	Co-morbid (n)	7.2 ± 3.2	10.1 ± 4.2	11.8 ± 4.3	13.2 ± 3.2
Sepsis	Age (years)	69.1 ± 17.5	72.9 ± 15.8	73.1 ± 13.9	72.6 ± 14.5
	CKD (%)	13.9	14.8	13.8	22.4
	Co-morbid (n)	10.5 ± 3.8	12.4 ± 3.3	12.9 ± 3.0	14.0 ± 2.6
UTI	Age (years)	66.5 ± 22.0	76.4 ± 14.4	75.1 ± 13.5	72.9 ± 14.6
	CKD (%)	14.9	14.2	10.1	17.0
	Co-morbid (n)	8.5 ± 4.2	11.5 ± 3.6	12.2 ± 3.5	13.7 ± 2.8

Overall	**Age (years)**	69.2 ± 17.2	72.3 ± 15.4	73.5 ± 14.6	71.4 ± 15.3
	CKD (%)	11.4	11.6	11.3	15.6
	Co-morbid (n)	9.1 ± 4.0	11.8 ± 3.8	12.4 ± 3.5	13.5 ± 2.9

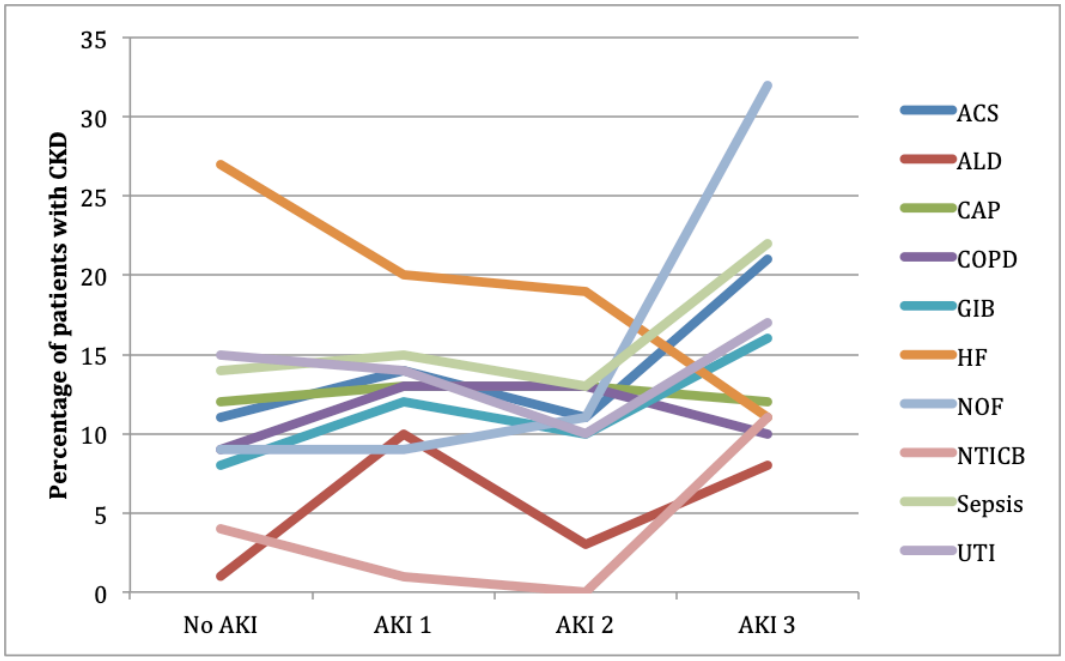
Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection, AKI – acute kidney injury and stage 0, stage 1, 2 or 3, n – number of patient

Figure 4-3 Mean patient age by diagnosis in different stages of AKI



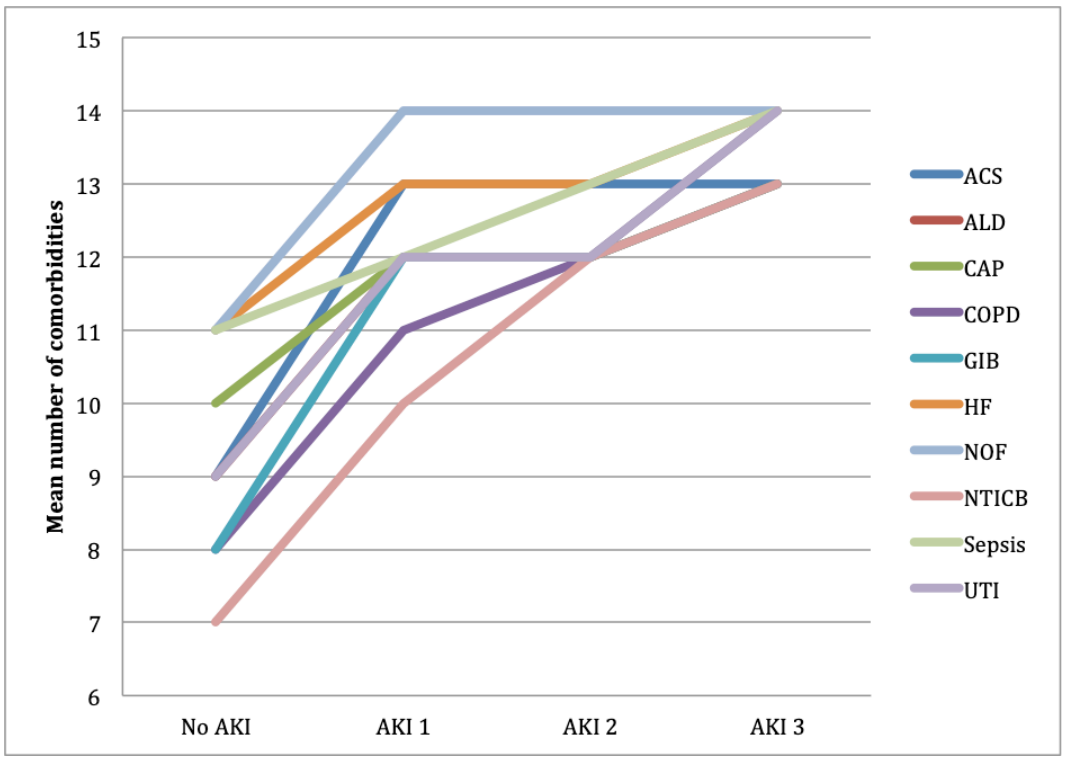
Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection

Figure 4-4 Percentage of patients with CKD in different stages of AKI



Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection

Figure 4-5 Mean numbers of comorbidities per patient by diagnosis in different stages of AKI



Key: ACS – acute coronary syndrome, ALD – alcoholic liver disease, CAP – community-acquired pneumonia, COPD – chronic obstructive pulmonary disease, HF – heart failure, GIB – gastro-intestinal bleed, sepsis – sepsis (any source). NTICB- Non-Traumatic Intra Cranial Bleed, NOF - Fractured neck of femur, UTI – urinary tract infection

4.6 Discussion

Overall, the results show that as AKI stage increases the risk of mortality generally increases and, in comparison to patients without AKI, any stage of AKI increases the risk or proportion of mortality within the selected admission diagnoses. Overall hospital mortality (3.4%) is comparable to previous studies (3.2%). However, our in-patient mortality in the selected diagnoses was higher. Here, in our study, there was a mortality of 19.3% for stage 1, 31.7% for stage 2 and 42.3% for stage 3 AKI. In comparison, Selby's previous study showed a mortality of 16.3% in stage 1, 33% in stage 2 and 36.1% in stage 3 AKI.[14] This is probably due to the differences in the underlying diagnoses, as our diagnoses were chosen not only for their admission frequency but also for their high rate of AKI.

There was a significant proportion of mortality in both AKI 2 and AKI 3 within each diagnosis. Around half of the patients admitted with heart failure, community-acquired pneumonia, COPD, alcoholic liver disease, sepsis or fractured necks of femurs died if an AKI 3 complicated their admission. While a retrospective observational study cannot infer causality, one could hypthesize that this is owing to the high frequency of stable admissions with these diagnoses, and that it is often rare for there to be haemodynamic compromise which would lead to AKI 3.

Interestingly, the percentages of patients with acute coronary syndrome and heart failure who suffered an AKI 2 or 3 and subsequently died were very similar (50.0% versus 47.4% in heart failure, and 36.5% versus 33.3% in acute coronary syndrome). The OR of death in AKI 2 was also similar to the OR of death in AKI 3 in both HF and ACS in comparison to no AKI. This finding was distinct from all other admission diagnoses. Also AKI 2 appears worse than AKI 3 in heart failure in comparison to patients without AKI, despite their being fewer patients with CKD in the AKI 3 group. Organ cross talk and the cardiorenal axis is likely to be at the root

of this finding. Again many patients who are admitted with ACS or heart failure do not have AKI, and increasing stages of AKI may suggest significant haemodynamic compromise due to ‘pump failure’ in cardiogenic shock or failure of response to diuretic therapy.

A higher proportion of patients with non-traumatic intracranial bleeds died without AKI. That suggests their mode of death did not involve sepsis or other haemodynamic compromise. They were younger and had less CKD than almost all other patient groups in this study, and their mode of death may have been quicker than other groups, with admission diagnoses that may have been terminal or pre-terminal. There was a significant worsening of mortality in most other groups as AKI stages progressed. This worsening was particularly pronounced in patients admitted with fractured neck of femur or COPD. In these two groups most admissions were not associated with AKI, and therefore the complication of AKI 3 represented significant haemodynamic compromise either through surgery or sepsis: this probably contributed to the significant increase in risk of mortality with increase in AKI stage.

Sepsis wasn’t the most significant admission diagnosis that contributed to mortality. This is probably owing to the coding of sepsis as an admission diagnosis, and may not reflect the subsequent causal diagnosis or severity of sepsis.

AKI 1 and AKI 2 had similar risks of death in patients admitted with GI bleed in comparison to no AKI or in comparison to other stages of AKI. In patients admitted with alcoholic liver disease AKI 1 was not a significant risk for mortality in comparison to no AKI or in comparison to other stages of AKI. This is probably owing to the mean age of the patients being the youngest in this study, and the fact that they had some of the lowest proportions of CKD.

Of particular novelty in this analysis, we have demonstrated that AKI 3 is not always, or not always significantly, associated with greater mortality in comparison to AKI 2. Those diagnoses in which AKI 3 was associated with higher mortality than AKI 2 were those in which patients were admitted with community-acquired pneumonia, urinary tract infections and fracture necks of femurs. There was no significant difference in age between these three diagnoses or the AKI stage severity that was linked to mortality.

4.6.1 Limitations

Salford Royal NHS Foundation Trust has a long history of digital excellence and has won awards for digital maturity. However, coding practice and the usage ICD 10 codes are prone to incompleteness or redundancy in primary care contexts. This may affect the categories of diagnosis and count of comorbidities.

Causality cannot be inferred in a retrospective observational study. It may well be that there are some more important factors at work, such as urine output, low bicarbonate or hyperkalaemia, that will help better delineate risk in AKI 2 versus AKI 3.

There is no formal assessment of frailty in this data. Accurate measurements of frailty cannot be made and corrected for with the present quantitative data (such as number of comorbidities). Salford Royal has now introduced clinical frailty scoring, and this will be available to include in the model for analysis of prospective data.

4.7 Conclusion

The cause of AKI heterogeneous, and so is its effect. In the majority of cases, an AKI is associated with a poor outcome, and this becomes increasingly likely with a more severe AKI (however this differs between diagnoses). Mortality outcomes in AKI 1 and 2 are comparable in patients with gastrointestinal bleeds and AKI 2 and 3 are comparable in patients with heart failure and acute coronary syndrome. The present work shows that there are sufficient differences between diagnoses that patients should not be grouped together in AKI stages unless the frequency of the end point necessitates this. For example, patients with heart failure need not necessarily have a change in their management strategy if their AKI stage increases from an AKI stage 2 to 3, as this does not reflect a worsening prognosis. This reflects the changing landscape of cardiorenal management and may support continuation rather than down-titration of medication in patients with heart failure. The present work encourages clinicians to consider individual patient risk and create personalized and tailored care plans to improve outcomes in AKI.

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Chapter 5

The influence of multiple episodes of acute kidney injury on survival and progression to end stage kidney disease in patients with chronic kidney disease

5.1 Rationale

The purpose of this chapter was to understand the effect of multiple episodes of acute kidney injury (AKI) in patients with pre-existing chronic kidney disease (CKD) in terms of CKD disease progression. This study grouped patients by different primary renal diseases, smoking and alcohol status, gender and age to see if there were differing patterns in terms of effect on rate of progression to renal replacement therapy, death or even further AKI and its relative severity. This work fed into the rationale underpinning the AKI intervention quality improvement work in chapter 6, by allowing us to better understand factors affecting AKI and CKD progression and risk factors for AKI.

This manuscript has already been published in PLOS and presented at the European Renal Association in Budapest in 2019, where one the best abstract award and a travel grant.
PLOS DOI: 10.1371/journal.pone.0219828

5.2 Abstract

Background

Acute kidney injury (AKI) and chronic kidney disease (CKD) are common syndromes associated with significant morbidity, mortality and cost. The extent to which repeated AKI episodes may cumulatively affect the rate of progression of all-cause CKD has not previously been investigated. In this study, we explored the hypothesis that repeated episodes of AKI increase the rate of renal functional deterioration loss in patients recruited to a large, all-cause CKD cohort.

Methods

Patients from the Salford Kidney Study (SKS) were considered. Application of KDIGO criteria to all available laboratory measurements of renal function identified episodes of AKI. A competing risks model was specified for four survival events: Stage 1 AKI; stage 2 or 3 AKI; dialysis initiation or transplant before AKI event; death before AKI event. The model was adjusted for patient age, gender, smoking status, alcohol intake, diabetic status, cardiovascular co-morbidities, and primary renal disease. Analyses were performed for patients' first, second, and third or more AKI episodes.

Results

A total of 48,338 creatinine measurements were available for 2287 patients (median 13 measures per patient [IQR 6-26]). There was a median age of 66.8years, median eGFR of 28.4 and 31.6% had type 1 or 2 diabetes. Six hundred and forty three (28.1%) patients suffered one or more AKI events; 1000 AKI events (58% AKI 1) in total were observed over a median follow-up of 2.6 years [IQR 1.1-3.2]. In patients who suffered an AKI, a second AKI was more likely to be a stage 2 or 3 AKI than stage 1 [HR 2.04, p 0.01]. AKI events were associated with progression to RRT, with multiple episodes of AKI progressively increasing likelihood of progression to RRT [HR 14.4 after 1 episode of AKI, HR 28.4 after 2 episodes of AKI]. However, suffering one or more AKI events was not associated with an increased risk of mortality.

Conclusion

AKI events are associated with more rapid CKD deterioration as hypothesised, and also with a greater severity of subsequent AKI. However, our study did not find an association of AKI with increased mortality risk in this CKD cohort.

5.3 Introduction

Acute kidney injury (AKI) and chronic kidney disease (CKD) are highly prevalent syndromes that are based on the same spectrum. Both AKI and CKD are associated with significant morbidity, mortality and Healthcare cost.[1–3] AKI has an incidence of 12 - 18% in recent United Kingdom (UK) studies of hospitalized patients.[4,5] Occurrence was associated with subsequent longer in-patient stays, and with over 40,000 deaths per annum.[4] The cost of treating AKI is estimated at 1% of the annual NHS budget, more than £1 billion annually.[4]

CKD affects 8-11% of the adult population, and is increased in populations with metabolic or cardiovascular co-morbidities. Whilst some patients do have predictable loss of glomerular filtration rate (GFR) over time, rates of CKD progression are variable and often non-linear.[6,7] Several studies already report the relationship between recurrent AKI episodes and CKD.[8–10] Hence CKD as a risk factor for the development of AKI is well established.[5,11] Recent data suggest that this may be a circular relationship.[12] Indeed, non-recovery from AKI may be the precipitant to CKD.[11 - 13] Furthermore, episodes of AKI in CKD patients are associated with more rapid transition between stages of CKD and increased risk for progression to end stage renal disease (ESRD) and the need for renal replacement therapy (RRT).[14,15]

What requires further evaluation is the extent to which repeated AKI episodes have a cumulative effect on worsening CKD prognosis. Likewise, further research is required into whether the severity of AKI events influences the long-term CKD outcome.[16,17] We explored these theories in this study, alongside secondary aims such as determining whether there is a difference in likelihood of CKD progression after AKI between different primary renal diseases.

5.4 Methods

5.4.1 Patient population

This analysis was performed as part of the Salford Kidney Study (SKS). This is a prospective study of patients referred to a single, secondary care renal centre for

management of CKD. The centre serves a catchment population of 1.5 million people. All referred patients with CKD aged over 18 years and with capacity to provide informed consent are eligible for recruitment. In the non-dialysis cohort, patients who are expected to progress to RRT within six months of recruitment are not approached. All patients provide written informed consent. The study complies with the declaration of Helsinki and local ethical approval was obtained (current REC reference 15/NW/0818, North West - Greater Manchester South Research Ethics Committee). Patients selected for this analysis were those recruited between the study start date, 15th November 2000, and 28th February 2013.

5.4.2 Study protocol and data collection

The design of the non-dialysis component of the SKS has been described previously under its previous title of the Chronic Renal insufficiency Standards Implementation Study (CRISIS).[18] In brief, demographic and clinical information are obtained at baseline and thereafter on an annual basis by means of a structured patient questionnaire delivered by trained research nurses. Reported co-morbidities and health issues are validated by reference to clinical notes stored within the local electronic patient record (EPR), through communication with their primary care provider, or by other secondary care providers in cases where admission to outlying hospitals occurred. All patients have a standardised biochemical and haematological analysis performed on an annual basis. Additional laboratory data collected as part of routine clinical care are also available for analysis. The integrated informatics and laboratory systems mean that this collection of additional laboratory data included those specimens collected by other local healthcare providers, including in Primary Care. The results of this study therefore include data relating to community acquired and managed AKI as well as those managed in hospital.

The key collected data included in the model were: 1) demographic (age, gender, height, weight, ethnicity, postcode); 2) renal (primary cause of CKD); 3) co-morbid conditions (diabetes mellitus, major cardiovascular events, smoking history, alcohol intake); 4) biochemical (serum creatinine [all values occurring over follow up were available for download from the EPR]; estimated glomerular filtration rate [eGFR] calculated using the 4-variable MDRD equation concomitant with creatinine measurement, urine protein:creatinine ratio). Pre-defined end-points were: death or

initiation of chronic RRT (defined as the date of first session of chronic haemodialysis or peritoneal dialysis, or date of renal transplantation).

5.4.3 Definition of AKI

Episodes of AKI were retrospectively identified in the SKS non-dialysis CKD population according to the KDIGO definition of AKI, by analysis of all repeated measurements of serum creatinine in each patient. Measurement of urine output for the extended KDIGO criteria was not available for consideration.[19] Patients who suffered AKI 3 could be captured in SKS because acute renal organ support is a defined end point within the study.

The relative change (RC) in serum creatinine (SCr) between two successive measurements (t and s) is calculated according to $(SCr_t - SCr_s)/(SCr_s)$. The classification of AKI events are as follows

- Stage 1: $0.5 \leqslant RC < 1$ or an absolute increase in SCr $\geq$ 26.5 μmol/L;
- Stage 2: $1 \leqslant RC < 2$
- Stage 3: RC > 2 or SCr $\geq$ 353.6 μmol/L or initiation of renal replacement therapy

In cases where multiple flags occurred within 7 days, the attributed grade of AKI was determined by the nadir of renal function (i.e. the greatest increase in creatinine) during this period. Patients with serum creatinine measurements taken during dialysis had those values excluded. A team of three independent nephrology research fellows (MR, DV, HVA) reviewed all potential AKI episodes. Where there was disagreement, adjudication was performed by PK and JR.

5.4.4 Statistical methodology

Up to four time periods were considered for each patient in this analysis. These were: time from recruitment to first AKI event; time from first to second AKI event; time from second to third AKI event; time after third AKI event.

As both death and progression to RRT are competing risks for further AKI episodes, competing risks models, a cause-specific Cox-model, were specified at each time point. These models considered four survival events: AKI 1; AKI 2/3; RRT before *n*th AKI event; Death before *n*th AKI event.

In the competing risks models, parameters were estimated by partial likelihood.[22] Cumulative incidence plots were used to graphically explore survival, as these remain unbiased where there are more than two outcomes.

5.5 Results

5.5.1 Study population

There were 2287 patients recruited to the SKS at the time of analysis. There were 48,338 repeated measurements of eGFR, of which 42,861 (88.7%) were outpatient readings. A total of 9262 eGFR readings (19.2%) were excluded from calculations of eGFR slope due to their measurement being in the immediate peri-AKI period as defined in the methods section. The number of repeated measurements per patients ranged between 1 and 280, with a median of 13.

The majority of patients were Caucasian (96.2%), with a predominance of males (62%), 67% of patients were current or ex-smokers, 48% drank alcohol, and 20% had suffered a previous cardiovascular event. Age at recruitment ranged between 20.0 and 94.3 years (median = 66.8 years) with a mean baseline eGFR of 30.5 ml/min/1.73m^2. The most commonly coded cause of CKD was vascular (hypertension or renovascular disease; 24.6%), followed by glomerulonephritis (16.8%) and then diabetic renal disease (16.4%). Less common primary diseases were pyelonephritis (6.0%) and autosomal dominant polycystic kidney disease (ADPKD; 5.7%). These demographic details are shown in Table 5-1.

Table 5-1. Demographics of patient cohort

Variable	**Category/Statistics**	**Frequency (%)/Values**
Number of patients		2287
Total number of measurements		48,338
Location where blood sample taken	Inpatient Outpatient	5477 (11.3 %) 42,861 (88.7 %)

Gender	Female Male	873 (38.2 %) 1414 (61.8 %)
Ethnicity	Caucasian Other	2200 (96.2 %) 87 (3.8 %)
Base hospital (at study entry)	Salford Royal Foundation Trust Other	681 (29.8 %) 1606 (70.2 %)
Smoking	Never smoked Ex/current	749 (32.7 %) 1538 (67.3 %)
Alcohol consumption	No Yes (any intake)	1191 (52.1 %) 1096 (47.9 %)
Diabetes	No Type I or II	1565 (68.4 %) 722 (31.6 %)
Previous major cardiovascular events	No Yes	1832 (80.1 %) 455 (19.9 %)
Primary renal disease	Diabetes Glomerulonephritis Immune/vasculitis Polycystic Pyelonephritis Vascular Other	375 (16.4 %) 383 (16.8 %) 64 (2.8 %) 131 (5.7 %) 137 (6.0 %) 635 (27.8 %) 562 (24.6 %)
Baseline age (years)	Min 50th quantile (Median) Max	20 66.8 94.3
Number of repeated measurements	Min 50th quantile (Median) Max	1 13 280
Total follow-up (years elapsed between first and last	Min 50th quantile	0 2.6

measurements)	(Median) Max	 10.9
Baseline eGFR	Min 50th quantile (Median) Max	2.6 28.4 116.5
Censored		1360 (59.5 %)
Renal replacement therapy		356 (15.6 %)
Death (before RRT)		571 (30.0 %)

Several factors had a statistically significant association with baseline renal function. These included geographical variation, and variation between primary renal diseases. Vasculitis was associated with the highest baseline function (+4.43 ml/min/1.73m^2 compared to the population mean). Higher baseline kidney function was also seen in patients who reported alcohol consumption (+6.7%, +1.5 ml/min/1.73m^2). Lower baseline kidney function was associated with increasing age. For each year increase in age, mean kidney function decreased by 0.4% per year (-0.1 ml/min/1.73m^2). Lower levels of baseline renal function were seen in patients with diabetic renal disease (-19%, -5.9 ml/min/1.73m^2), ADPKD (-23%, -6.1 ml/min/1.73m^2), and chronic pyelonephritis (1%, -3.7 ml/min/1.73m^2).

Patient follow-up time ranged between 0 (i.e. only one creatinine measurement) and 10.9 years (median 2.56 years, IQR 1.09 – 4.60 years). 332 patients (14.5%) progressed to RRT, and 534 (23.3%) died prior to initiation of RRT. The incidence of RRT decreased over time, whilst incidence of death appeared constant (Figure 5-1). Administrative censoring occurred in 1338 cases (58.5%).

5.5.2 AKI episodes

In total, 1000 AKI events were observed within this dataset. The majority were AKI 1 (n=523, 52.3%), with 47.7% being AKI 2 or 3 (n=477). At least one AKI event was observed in 643 patients (28.1%). Of the first AKI events, 343 were AKI 1 (53.3%) and 300 were AKI 2 or 3 (46.7%). With each additional AKI episode, an increasing proportion were numerically more severe AKI (i.e. stage 2 or 3 rather

than AKI 1) compared to previous AKI events. Two or more AKI episodes were observed in 185 patients (8.1%). Of these second AKI events, 69 were AKI 1 (37.2%), and 116 were AKI 2 or 3 (62.7%, compared with 46.7% of first AKI as detailed above). Three or more AKI episodes were observed in 83 patients (3.6%). Of these third or more AKI events, 29 were AKI 1 (34.9%), and 54 AKI 2 or 3 (65.1%). This is shown in the consort diagram in Figure 5-2.

Figure 5-1. Cumulative incidence of outcome in the study population, RRT = renal replacement therapy

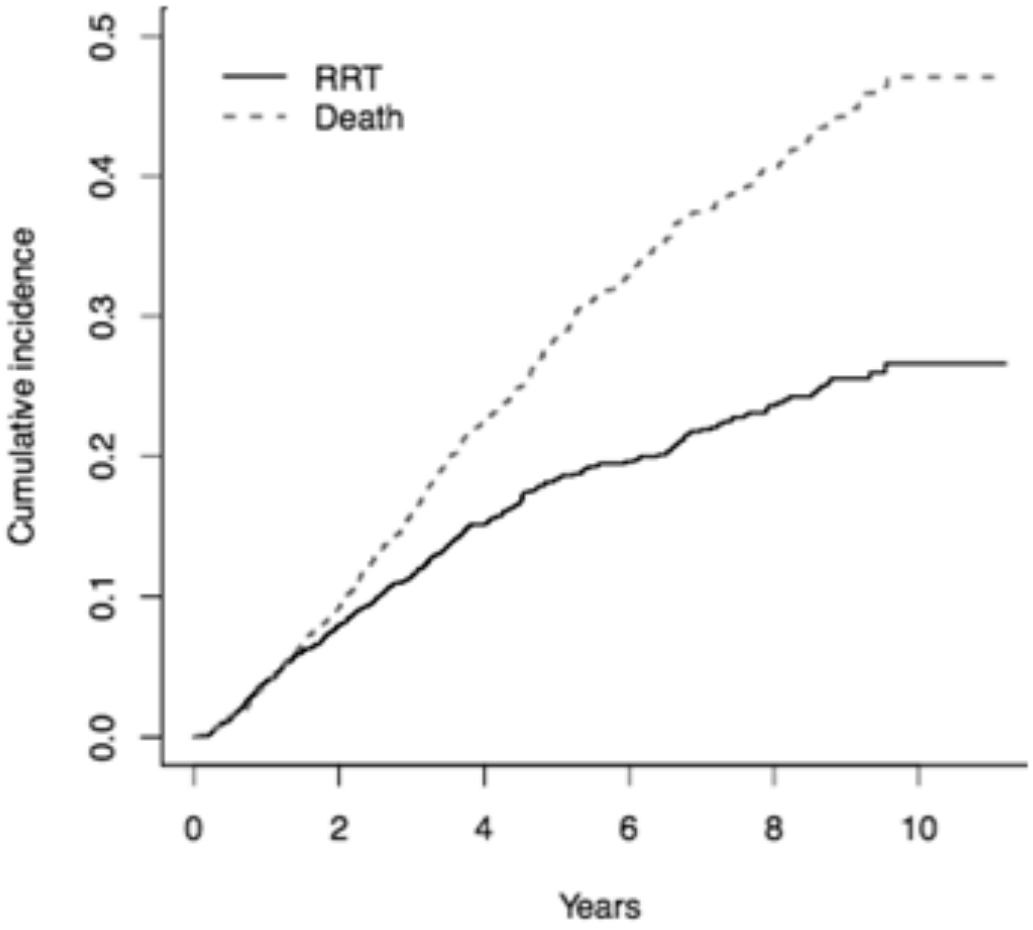


Figure 5-2. Consort diagram to show outcomes

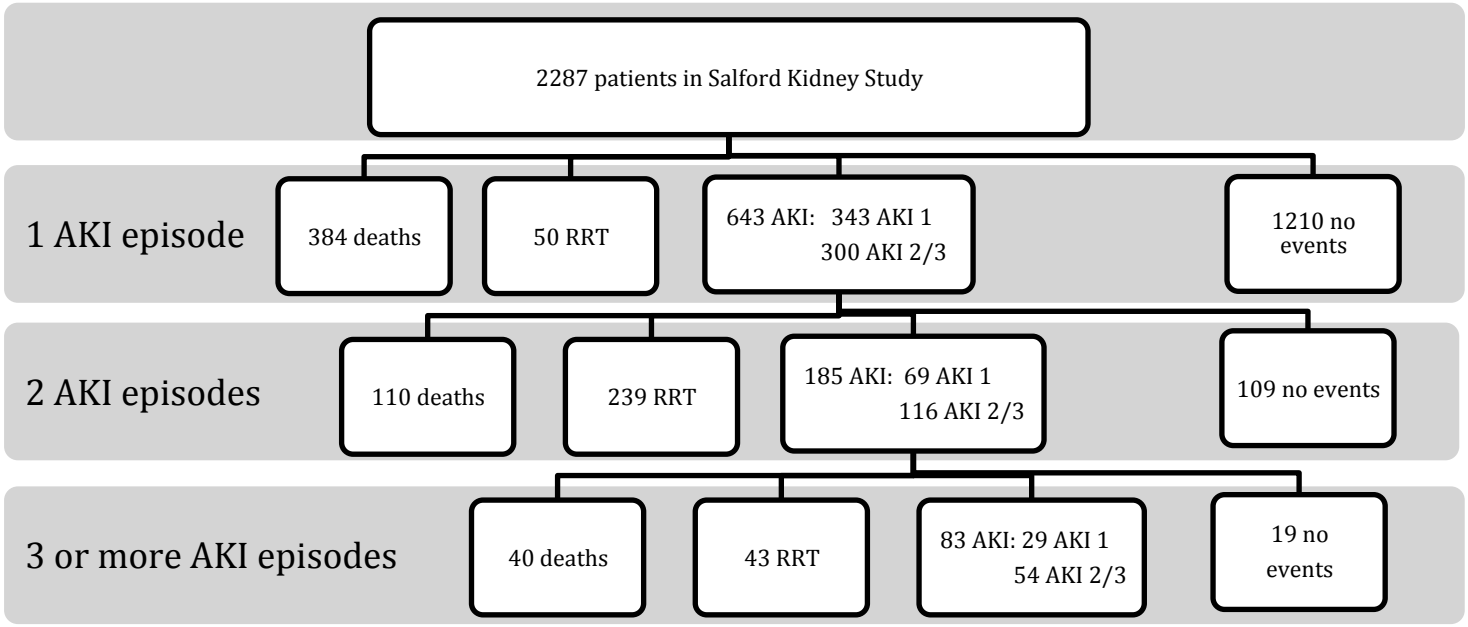
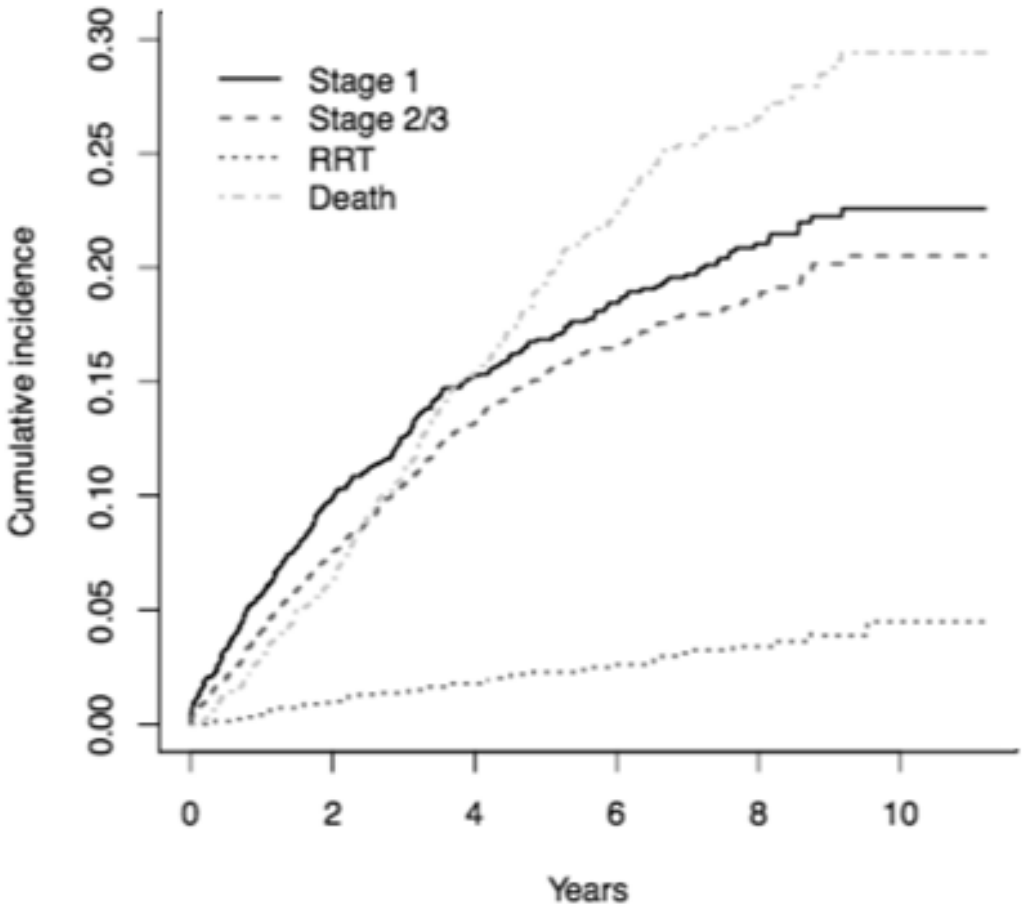


Figure key: AKI – acute kidney injury, RRT –renal replacement therapy

5.5.3 Survival analysis, first AKI event

50 patients (2.2%) progressed to chronic RRT prior to the first AKI event, and 384 (16.8%) died before suffering an AKI event (Figure 5-3). 643 patients went on to have one or more AKI events during follow up; 300 (13.1%) had an AKI stage 2 or 3, and 343 (15.0%) had a stage 1 AKI stage 1 but no stage 2 or 3 events. No outcome events were observed in 1210 patients (52.9%). These were administratively censored.

Figure 5-3. Cumulative incidences of first study end points in the Salford Kidney Study population, RRT = renal replacement therapy, 'Stage 1' and 'Stage 2/3' refer to first AKI event



Clinical factors associated with first event being AKI 1 were a smoking history (HR1.38; 95% CI 1.08 – 1.77, p=0.01), diabetic renal disease (HR 1.55; 95% CI 1.04 – 2.31, p=0.031) and autoimmune or vasculitic renal disease (HR 1.90; 95% CI 1.14 – 3.18, p=0.014). An increased risk for AKI stage 2 or 3 was associated with ADPKD (HR 2.23; 95% CI 1.46 – 3.39, p<0.001) and older age (HR 1.01 per year; 95% CI 1.01 – 1.02, p=0.015). Summary results for likelihood ratios for a first AKI event are presented in table 5-2 with complete results in table 5-2a.

Table 5-2. Summary of significant variables for stage of AKI

Variable	HR (95% CI)	p-value
Significant risk for stage of first AKI		
Stage 1 AKI		
Base hospital (tertiary centre)	2.31 (1.86, 2.86)	<0.001
Ex or current smoker	1.38 (1.08, 1.77)	0.01
Primary renal disease diabetes	1.55 (1.04, 2.31)	0.03
Primary renal disease immune or vasculitis	1.90 (1.14, 3.18)	0.01
Stage 2/3 AKI		
Baseline age (years)	0.99 (0.98, 1.00)	0.02
Primary renal disease polycystic kidneys	2.23 (1.46, 3.39)	<0.001
Significant risk for stage of second AKI		
Stage 1 AKI		
First AKI (stage 2/3)	0.49 (0.95, 0.85)	0.01
Ex or current smoker	0.65 (0.43, 1.00)	0.05
Stage 2/3 AKI		
Nil significantly associated		
Significant risk for stage of third or more AKI		
Stage 1 AKI		
Nil significantly associated		
Stage 2/3 AKI		
Nil significantly associated		

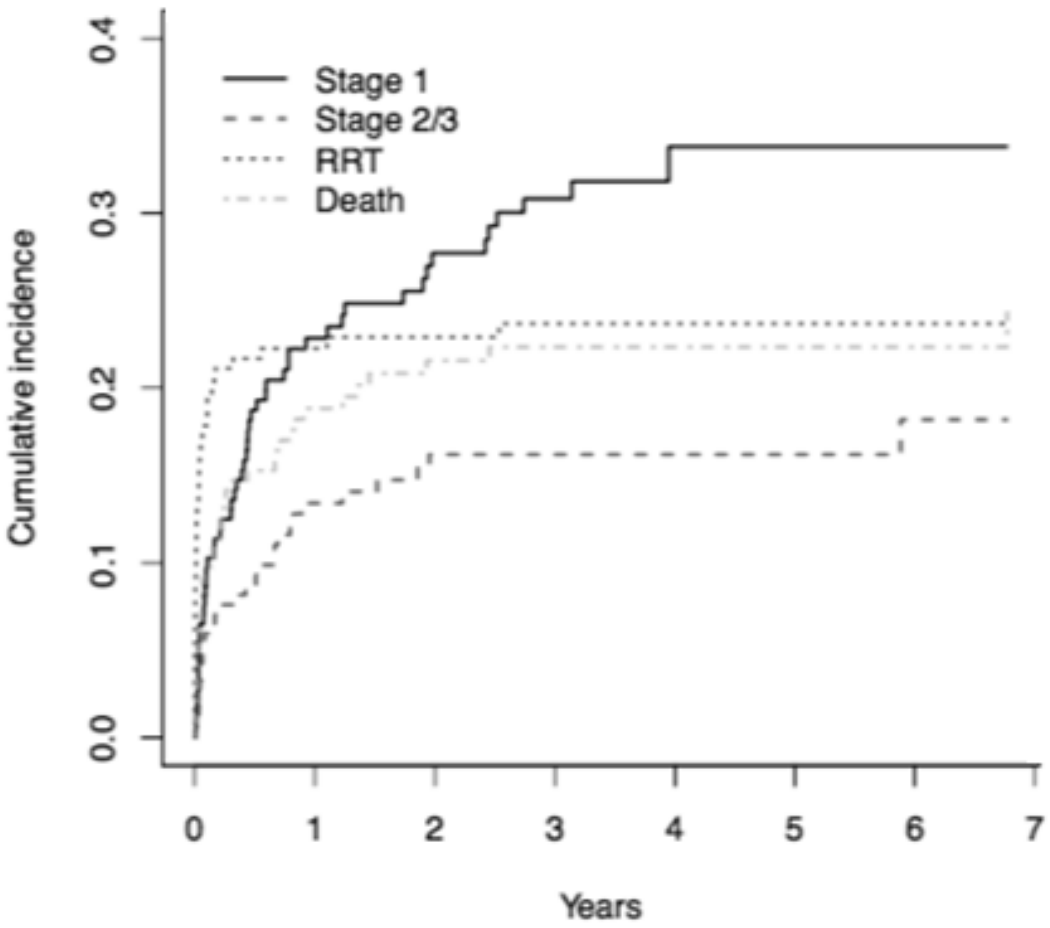
Table 5-2a. Partial likelihood estimates for the first AKI event. SE: standard error, HR: hazard ratio, CI: confidence interval.

Stage 1				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
Baseline age	0.00	0.00	1.00 (0.99, 1.01)	0.50
Base hospital (SRFT=1)	0.84	0.11	2.31 (1.86, 2.86)	<0.001
Gender (male=1)	-0.09	0.12	0.92 (0.73, 1.15)	0.46
Smoking (ex/current=1)	0.32	0.13	1.38 (1.08, 1.77)	0.01
Alcohol (any intake=1)	-0.22	0.11	0.80 (0.64, 1.00)	0.05
Diabetes (type I/II=1)	0.10	0.16	1.10 (0.81, 1.51)	0.55
Cardiovascular (yes=1)	0.17	0.14	1.19 (0.91, 1.55)	0.22
PRD (diabetes=1)	0.44	0.20	1.55 (1.04, 2.31)	0.03
PRD (GN=1)	0.11	0.18	1.12 (0.78, 1.61)	0.54
PRD (immune/vasc=1)	0.64	0.26	1.90 (1.14, 3.18)	0.01
PRD (polycystic=1)	-0.03	0.29	0.97 (0.55, 1.71)	0.92
PRD (pyelonephritis=1)	-0.12	0.26	0.89 (0.54, 1.47)	0.65
PRD (vascular=1)	-0.15	0.17	0.86 (0.62, 1.19)	0.37
Stage 2/3				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
Baseline age	-0.01	0.01	0.99 (0.98, 1.00)	0.02
Base hospital (SRFT=1)	-0.19	0.13	0.83 (0.64, 1.07)	0.15
Gender (male=1)	0.08	0.13	1.09 (0.85, 1.39)	0.52
Smoking (ex-current=1)	0.02	0.13	1.02 (0.80, 1.30)	0.90
Alcohol (any intake=1)	-0.07	0.12	0.94 (0.74, 1.18)	0.58
Diabetes (type I/II=1)	0.04	0.18	1.04 (0.73, 1.50)	0.82
Cardiovascular (yes=1)	0.02	0.17	1.02 (0.74, 1.41)	0.91
PRD (diabetes=1)	0.43	0.23	1.53 (0.97, 2.41)	0.07
PRD (GN=1)	0.14	0.19	1.15 (0.79, 1.67)	0.46
PRD (immune/vasc=1)	-0.27	0.38	0.76 (0.36, 1.60)	0.47
PRD (polycystic=1)	0.80	0.22	2.23 (1.46, 3.39)	<0.001
PRD (pyelonephritis=1)	-0.25	0.28	0.78 (0.45, 1.35)	0.37
PRD (vascular=1)	-0.04	0.19	0.96 (0.67, 1.40)	0.84

5.5.4 Survival analysis, second AKI event

Of the 643 patients who suffered a first AKI event, 185 (28.8%) then had a second AKI; 69 cases were AKI 1 (37.2%), and 116 were AKI 2 or 3 (62.7%, compared with 46.7% of first AKI as detailed above). There were 239 patients (37.2%) who progressed to chronic RRT before a second AKI occurred, and 110 (17.1%) died before a second AKI. A time dependent comparison of these events is shown in Figure 5-4. In 109 patients (16.9%) patients no further events occurred and were therefore administratively censored.

Figure 5-4. Cumulative incidences of study end points after any second acute kidney injury. RRT = renal replacement therapy. "Stage 1" and "Stage 2/3" refer to first AKI event



In the 185 patients who suffered a second AKI episode, patients who had suffered an AKI stage 2 or 3 (in comparison to an AKI 1) as their first event had a greater risk for their second event also being an AKI 2 or 3 (HR 2.04; 95% CI 1.18 – 3.45, p=0.011). No other clinical characteristics were significantly associated with risk for second AKI being stage 2 or 3 compared to stage 1. Summary results of likelihood ratios for factors associated with a second AKI event are presented in table 5-2 with complete results in table 5-2b.

Table 5-2b. Partial likelihood estimates for the second AKI event. SE: standard error, HR: hazard ratio, CI: confidence interval.

Stage 1				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
First AKI (stage 2/3=1)	-0.71	0.28	0.49 (0.95, 0.85)	0.01
Baseline age	0.01	0.01	1.01 (1.00, 1.02)	0.19
Base hospital (SRFT=1)	0.24	0.20	1.27 (0.85, 1.88)	0.24
Gender (male=1)	0.35	0.22	1.41 (0.92, 2.17)	0.11
Smoking (ex-current=1)	-0.43	0.22	0.65 (0.43, 1.00)	0.05
Alcohol (any intake=1)	0.05	0.20	1.05 (0.71, 1.55)	0.80
Diabetes (type I/II=1)	0.21	0.28	1.23 (0.71, 2.13)	0.45
Cardiovascular (yes=1)	0.16	0.24	1.17 (0.73, 1.88)	0.51
PRD (diabetes=1)	-0.15	0.35	0.86 (0.43, 1.72)	0.68
PRD (GN=1)	-0.18	0.32	0.84 (0.45, 1.55)	0.57
PRD (immune/vasc=1)	-0.06	0.51	0.95 (0.35, 2.57)	0.91
PRD (polycystic=1)	-0.22	0.55	0.81 (0.28, 2.36)	0.70
PRD (pyelonephritis=1)	-0.04	0.44	0.96 (0.41, 2.28)	0.93
PRD (vascular=1)	-0.37	0.29	0.69 (0.39, 1.23)	0.21
Stage 2/3				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
First AKI (stage 2/3=1)	0.13	0.29	1.14 (0.64, 2.02)	0.66
Baseline age	0.00	0.01	1.00 (0.98, 1.02)	0.80
Base hospital (SRFT=1)	-0.02	0.26	0.98 (0.59, 1.63)	0.94

Gender (male=1)	0.22	0.29	1.24 (0.70, 2.20)	0.45
Smoking (ex-current=1)	0.39	0.31	1.48 (0.80, 2.74)	0.21
Alcohol (any intake=1)	0.15	0.26	1.16 (0.70, 1.92)	0.56
Diabetes (type I/II=1)	0.19	0.39	1.21 (0.56, 2.60)	0.63
Cardiovascular (yes=1)	-0.55	0.37	0.58 (0.28, 1.189)	0.14
PRD (diabetes=1)	0.21	0.50	1.23 (0.46, 3.29)	0.68
PRD (GN=1)	0.11	0.42	1.12 (0.49, 2.53)	0.79
PRD (immune/vasc=1)	0.32	0.68	1.38 (0.36, 5.27)	0.64
PRD (polycystic=1)	-0.41	0.78	0.66 (0.15, 3.02)	0.60
PRD (pyelonephritis=1)	0.47	0.56	1.60 (0.54, 4.77)	0.40
PRD (vascular=1)	0.24	0.39	1.27 (0.60, 2.73)	0.53

5.5.5 Survival analysis, three or more AKI events

Of the 185 patients who had suffered two AKI episodes, 83 (44.9%) of these patients went on to have three or more episodes of AKI. 29 (15.7%) had a further AKI stage 1, 54 (29.2%) had a further AKI stage 2 or 3. 43 patients (23.2%) progressed to chronic RRT before a third AKI event, and 40 (21.6%) died before a third AKI event. There were no statistically significant characteristics associated with the risk for a third AKI event of any stage. Summary results of likelihood ratios for factors associated with a third AKI event are presented in table 5-2 with complete results in table 5-2c.

Table 5-2c. Partial likelihood estimates for a third or more AKI events. SE: standard error, HR: hazard ratio, CI: confidence interval.

Stage 1				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
Second AKI (stage 2/3=1)	-0.33	0.38	0.72 (0.34, 1.51)	0.38
Baseline age	0.00	0.01	1.00 (0.97, 1.02)	0.82

Base hospital (SRFT=1)	-0.24	0.33	0.79 (0.41, 1.52)	0.48
Gender (male=1)	-0.26	0.34	0.77 (0.40, 1.49)	0.44
Smoking (ex-current=1)	-0.21	0.33	0.81 (0.43, 1.55)	0.53
Alcohol (any intake=1)	0.09	0.30	1.10 (0.61, 1.99)	0.76
Diabetes (type I/II=1)	-0.54	0.43	0.59 (0.25, 1.35)	0.21
Cardiovascular (yes=1)	0.51	0.38	1.67 (0.79, 3.51)	0.18
PRD (diabetes=1)	0.71	0.53	2.03 (0.72, 5.68)	0.18
PRD (GN=1)	0.21	0.51	1.23 (0.45, 3.34)	0.69
PRD (immune/vasc=1)	0.74	0.73	2.09 (0.50, 8.67)	0.31
PRD (polycystic=1)	-0.34	1.08	0.71 (0.09, 5.92)	0.75
PRD (pyelonephritis=1)	-0.21	0.71	0.81 (0.20, 3.25)	0.77
PRD (vascular=1)	0.58	0.45	1.79 (0.74, 4.32)	0.20
Stage 2/3				
Variable	**Estimate**	**SE**	**HR (95% CI)**	**p-value**
Second AKI (stage 2/3=1)	-0.26	0.49	0.77 (0.30, 2.02)	0.60
Baseline age	0.00	0.01	1.00 (0.97, 1.03)	0.81
Base hospital (SRFT=1)	0.88	0.48	2.40 (0.95, 6.10)	0.07
Gender (male=1)	0.13	0.46	1.14 (0.46, 2.81)	0.78
Smoking (ex-current=1)	0.04	0.48	1.04 (0.41, 2.68)	0.93
Alcohol (any intake=1)	-0.63	0.45	0.54 (0.22, 1.30)	0.17
Diabetes (type I/II=1)	-1.41	0.80	0.25 (0.05, 1.18)	0.08
Cardiovascular (yes=1)	-0.50	0.66	0.61 (0.17, 2.23)	0.45
PRD (diabetes=1)	1.17	0.93	3.21 (0.52, 19.89)	0.21
PRD (GN=1)	0.50	0.65	1.65 (0.46, 5.93)	0.45
PRD (immune/vasc=1)	0.98	1.19	2.66 (0.26, 27.28)	0.41
PRD (polycystic=1)	0.94	0.78	2.56 (0.56, 11.76)	0.23
PRD (pyelonephritis=1)	-0.24	0.91	0.78 (0.13, 4.70)	0.79
PRD (vascular=1)	0.32	0.66	1.38 (0.38, 5.00)	0.63

5.5.6 Survival analysis, mortality

Baseline factors significantly associated with risk for death prior to the first AKI episode included increased age (HR 1.08 [1.07 – 1.09] per year, p<0.001), male gender (HR 1.27 [1.01 – 1.59], p=0.039), smoking (HR 1.39 [1.09 – 1.77], p=0.008), diabetes mellitus (HR 1.58 [1.23 – 2.03], p=<0.001) and pre-existing cardiovascular disease (HR 1.36 [1.09 – 1.69], p=0.007). Alcohol consumption was associated with a lower risk of death (HR 0.77 [0.62 – 0.95], p=0.017). A summary is presented in table 5-3 with the full model found in table 5-3a.

Table 5-3. Summary of significant variables for risk of death

Variable	HR (95% CI)	p-value
Significant risk for death prior to first AKI		
Baseline age (years)	1.08 (1.07, 1.09)	<0.001
Base hospital (tertiary centre)	0.60 (0.48, 0.72)	<0.001
Male gender	1.27 (1.01, 1.59)	0.04
Ex or current smoker	1.39 (1.09, 1.77)	0.01
Any alcohol intake	0.77 (0.62, 0.95)	0.02
Diabetes (type I/II)	1.58 (1.23, 2.03)	<0.001
Major cardiovascular event	1.36 (1.09, 1.70)	0.01
Significant risk for death prior to second AKI		
Baseline age (years)	1.05 (1.03, 1.07)	<0.001
Major cardiovascular event	1.52 (1.00, 2.32)	0.05
Primary renal disease diabetes	2.14 (0.99, 4.62)	0.05
Primary renal disease immune or vasculitis	3.41 (1.29, 9.03)	0.01
Primary renal disease vascular	2.10 (1.12, 3.61)	0.02
Significant risk for death prior to third or more AKI		
Baseline age (years)	1.06 (1.02, 1.10)	<0.001
Any alcohol intake	2.28 (1.08, 4.84)	0.03
Major cardiovascular event	2.80 (1.27, 6.20)	0.01
Primary renal disease glomerulonephritis	3.56 (1.10, 11.54)	0.03

Table 5-3a. Partial likelihood estimates for death prior to the first AKI event.

SE: standard error, HR: hazard ratio, CI: confidence interval

Variable	Estimate	SE	HR (95% CI)	p-value
Baseline age	0.08	0.01	1.08 (1.07, 1.09)	0.00
Base hospital (SRFT=1)	-0.51	0.12	0.60 (0.48, 0.72)	0.00
Gender (male=1)	0.24	0.12	1.27 (1.01, 1.59)	0.04
Smoking (ex-current=1)	0.33	0.12	1.39 (1.09, 1.77)	0.01
Alcohol (any intake=1)	-0.26	0.11	0.77 (0.62, 0.95)	0.02
Diabetes (type I/II=1)	0.46	0.13	1.58 (1.23, 2.03)	0.00
Cardiovascular (yes=1)	0.31	0.11	1.36 (1.09, 1.70)	0.01
PRD (diabetes=1)	-0.03	0.19	0.97 (0.67, 1.40)	0.87
PRD (GN=1)	-0.07	0.19	0.93 (0.64, 1.37)	0.72
PRD (immune/vasc=1)	-0.56	0.46	0.57 (0.23, 1.41)	0.22
PRD (polycystic=1)	-0.27	0.35	0.77 (0.38, 1.53)	0.45
PRD (pyelonephritis=1)	-0.14	0.27	0.87 (0.51, 1.47)	0.61
PRD (vascular=1)	0.08	0.14	1.08 (0.83, 1.42)	0.56

Following the first AKI episode and prior to the second AKI, only patient age remained significantly associated with risk for death (HR 1.053 [1.033 – 1.073], p=<0.001). An increased risk for death was associated with immune mediated (HR 3.411 [1.288 – 9.034], p=0.014) and vascular causes of kidney disease (HR 2.009 [1.119 – 3.609], p=0.020). A summary is found in 5- 3 with the full model output found in table 5-3b.

Table 5-3b. Partial likelihood estimates for death prior to the second AKI event SE: standard error, HR: hazard ratio, CI: confidence interval.

Variable	Estimate	SE	HR (95% CI)	p-value
First AKI (stage 2/3=1)	0.32	0.23	1.38 (0.88, 2.16)	0.16
Baseline age	0.05	0.01	1.05 (1.03, 1.07)	0.00
Base hospital (SRFT=1)	-0.14	0.21	0.87 (0.57, 1.31)	0.50
Gender (male=1)	0.02	0.22	1.02 (0.67, 1.57)	0.91
Smoking (ex-current=1)	0.22	0.26	1.25 (0.76, 2.06)	0.39
Alcohol (any intake=1)	-0.31	0.21	0.73 (0.49, 1.10)	0.14
Diabetes (type I/II=1)	-0.17	0.28	0.85 (0.49, 1.45)	0.54
Cardiovascular (yes=1)	0.42	0.22	1.52 (1.00, 2.32)	0.05
PRD (diabetes=1)	0.76	0.39	2.14 (0.99, 4.62)	0.05
PRD (GN=1)	0.17	0.39	1.18 (0.55, 2.54)	0.67
PRD (immune/vasc=1)	1.23	0.50	3.41 (1.29, 9.03)	0.01
PRD (polycystic=1)	-0.18	0.76	0.84 (0.19, 3.68)	0.81
PRD (pyelonephritis=1)	0.15	0.64	1.16 (0.34, 4.04)	0.81
PRD (vascular=1)	0.70	0.30	2.10 (1.12, 3.61)	0.02

For patients who survived following a second episode of AKI, age (HR 1.059 [1.021 – 1.097], p=0.002), alcohol (HR 2.284 [1.078 – 4.840], p=0.031), cardiovascular disease (HR 2.800 [1.265 – 6.200], p=0.011), and glomerulonephritis as primary disease (HR 3.564 [1.101 – 11.541], p=0.034) were significantly associated with risk for death. A summary is presented in table 5-3 with the full model output found in table 5-3c.

Table 5-3c. Partial likelihood estimates for death prior to the third AKI event. SE: standard error, HR: hazard ratio, CI: confidence interval.

Variable	Estimate	SE	HR (95% CI)	p-value
Second AKI (stage 2/3=1)	-0.38	0.42	0.69 (0.30, 1.55)	0.37
Baseline age	0.06	0.02	1.06 (1.02, 1.10)	0.00
Base hospital (SRFT=1)	0.15	0.43	1.16 (0.50, 2.70)	0.74
Gender (male=1)	-0.64	0.38	0.53 (0.25, 1.10)	0.09
Smoking (ex-current=1)	0.03	0.40	1.03 (0.47, 2.27)	0.94
Alcohol (any intake=1)	0.83	0.38	2.28 (1.08, 4.84)	0.03
Diabetes (type I/II=1)	-0.17	0.47	0.85 (0.34, 2.12)	0.73
Cardiovascular (yes=1)	1.03	0.41	2.80 (1.27, 6.20)	0.01
PRD (diabetes=1)	1.07	0.59	2.90 (0.91, 9.22)	0.07
PRD (GN=1)	1.27	0.60	3.56 (1.10, 11.54)	0.03
PRD (immune/vasc=1)	0.53	1.15	1.69 (0.18, 16.13)	0.65
PRD (vascular=1)	0.92	0.50	2.52 (0.95, 6.69)	0.06

5.5.7 Survival analysis, renal replacement therapy

In the period after a first AKI episode, those patients whose first episode of AKI was stage 2 or 3 had a fourteen-fold increased risk for RRT during follow up compared to patients who had suffered an AKI 1 (HR 14.46 [9.56 – 21.87], p <0.001). In the period after a second AKI episode (n = 185), those patients whose second AKI had been stage 2 or 3 had a twenty-eight fold increase in risk for progression to RRT compared to AKI stage 1 patients (HR 28.39 [9.71 – 82.99], p <0.001). A summary of complete results for all model outputs for RRT as outcome for these two time periods, and for prior to any AKI, are shown in table 5-4 with complete results in the tables 5-4a, 5-4b and 5-4c.

Table 5-4. Summary of significant variables for risk of RRT

Variable	HR (95% CI)	p-value
Significant risk for RRT prior to first AKI		
Baseline age (years)	0.97 (0.95, 0.99)	0.01
Base hospital (tertiary centre)	0.45 (0.21, 0.96)	0.04
Significant risk for RRT prior to second AKI		
First AKI (stage 2/3)	14.46 (9.56, 21.87)	<0.001
Baseline age (years)	0.99 (0.98, 1.00)	0.01
Base hospital (tertiary centre)	0.44 (0.31 0.62)	<0.001
Primary renal disease polycystic kidneys	2.11 (1.33, 3.33)	<0.001
Primary renal disease pyelonephritis	2.29 (1.28, 4.07)	0.01
Significant risk for RRT prior to third or more AKI		
Second AKI (stage 2/3)	28.39 (9.71, 83.00)	<0.001
Base hospital (tertiary centre)	0.34 (0.16, 0.73)	0.01
Diabetes (type I/II)	0.22 (0.06, 0.89)	0.03

Table 5-4a. Partial likelihood estimates for RRT prior to the first AKI event.
SE: standard error, HR: hazard ratio, CI: confidence interval.

Variable	Estimate	SE	HR (95% CI)	p-value
Baseline age	-0.03	0.01	0.97 (0.95, 0.99)	0.01
Base hospital (SRFT=1)	-0.80	0.39	0.45 (0.21, 0.96)	0.04
Gender (male=1)	-0.02	0.30	0.98 (0.54, 1.78)	0.94
Smoking (ex-current=1)	0.61	0.33	1.84 (0.97, 3.47)	0.06
Alcohol (any intake=1)	-0.18	0.29	0.83 (0.47, 1.48)	0.54
Diabetes (type I/II=1)	-0.27	0.55	0.76 (0.26, 2.22)	0.62
Cardiovascular (yes=1)	-1.09	0.61	0.34 (0.10, 1.12)	0.08
PRD (diabetes=1)	1.17	0.67	3.21 (0.87, 11.81)	0.08
PRD (GN=1)	0.16	0.51	1.17 (0.43, 3.17)	0.76
PRD (immune/vasc=1)	0.05	0.81	1.06 (0.22, 5.16)	0.95
PRD (polycystic=1)	0.87	0.57	2.39 (0.79, 7.26)	0.12
PRD (pyelonephritis=1)	-0.24	0.71	0.79 (0.20, 3.16)	0.74
PRD (vascular=1)	0.74	0.49	2.10 (0.80, 5.51)	0.13

Table 5-4b. Partial likelihood estimates for RRT prior to the second AKI event.
SE: standard error, HR: hazard ratio, CI: confidence interval.

Variable	Estimate	SE	HR (95% CI)	p-value
First AKI (stage 2/3=1)	2.67	0.21	14.46 (9.56, 21.87)	0.00
Baseline age	-0.01	0.01	0.99 (0.98, 1.00)	0.01
Base hospital (SRFT=1)	-0.83	0.18	0.44 (0.31 0.62)	0.00
Gender (male=1)	0.24	0.15	1.27 (0.95, 1.70)	0.10
Smoking (ex-current=1)	0.17	0.15	1.19 (0.90, 1.58)	0.23
Alcohol (any intake=1)	-0.03	0.14	0.97 (0.74, 1.27)	0.82
Diabetes (type I/II=1)	0.21	0.24	1.23 (0.77, 1.97)	0.39
Cardiovascular (yes=1)	-0.16	0.21	0.85 (0.57, 1.28)	0.44
PRD (diabetes=1)	0.20	0.28	1.22 (0.70, 2.13)	0.49
PRD (GN=1)	0.13	0.22	1.14 (0.74, 1.76)	0.56

PRD (immune/vasc=1)	0.32	0.42	1.38 (0.61, 3.14)	0.44
PRD (polycystic=1)	0.75	0.23	2.11 (1.33, 3.33)	0.00
PRD (pyelonephritis=1)	0.83	0.29	2.29 (1.28, 4.07)	0.01
PRD (vascular=1)	0.11	0.23	1.12 (0.71, 1.77)	0.63

Table 5-4c. Partial likelihood estimates for RRT prior to the third AKI event.

SE: standard error, HR: hazard ratio, CI: confidence interval.

Variable	Estimate	SE	HR (95% CI)	p-value
Second AKI (stage 2/3=1)	3.35	0.55	28.39 (9.71, 83.00)	0.00
Baseline age	-0.03	0.01	0.98 (0.95, 1.00)	0.06
Base hospital (SRFT=1)	-1.08	0.39	0.34 (0.16, 0.73)	0.01
Gender (male=1)	0.02	0.43	1.02 (0.44, 2.39)	0.96
Smoking (ex-current=1)	0.18	0.39	1.20 (0.56, 2.57)	0.64
Alcohol (any intake=1)	0.07	0.39	1.07 (0.50, 2.30)	0.85
Diabetes (type I/II=1)	-1.50	0.70	0.22 (0.06, 0.89)	0.03
Cardiovascular (yes=1)	0.76	0.58	2.14 (0.68, 6.72)	0.19
PRD (diabetes=1)	1.01	0.88	2.74 (0.49, 15.43)	0.25
PRD (GN=1)	0.49	0.60	1.63 (0.51, 5.22)	0.42
PRD (immune/vasc=1)	0.55	0.88	1.73 (0.31, 9.73)	0.54
PRD (polycystic=1)	-0.14	0.86	0.87 (0.16, 4.65)	0.87
PRD (pyelonephritis=1)	0.27	0.80	1.30 (0.27, 6.30)	0.74
PRD (vascular=1)	0.27	0.54	1.31 (0.46, 3.79)	0.61

5.6 Discussion

This study presents several findings relevant to the prognosis of patients with chronic kidney disease who suffer acute kidney injury. We have confirmed the findings of previous studies that have shown patient age to be a risk factor for the development of AKI.[13] Our findings add to this by suggesting that age could be considered as a dynamic risk factor relevant to stage of AKI. Given that many risk stratification tools for AKI define age greater than 65 years[23] as a risk factor, it may be that this affords sensitivity to AKI 1 at the risk of failing to identify younger patients with an increased risk for more severe AKI.

In the SKS cohort the primary renal diagnoses included in the model are those with the greatest numbers (over 130 individuals in each) or of particular interest (vasculitis). The other diagnoses are of multiple etiologies including IgA, focal segmental glomerulosclerosis, membranous, haemolytic uraemic syndrome, lupus nephritis, membranoproliferative glomerulonephritis, drug-induced or amyloid. It is reasonable to consider diabetes and diabetic renal disease as separate as diabetic nephropathy may not be the cause of the primary renal disease in all patients with diabetes. In total 13.2% of all diagnoses in the SKS have an unknown primary renal disease. The lower observed percentages of patients with diabtetes (31.6%) or primary renal diagnoses of diabetes (16.4%) than in other studies may reflect the predominantly Caucasian ethnicity (96.2%) within the SKS group.

Previous analyses from the SKS[24] and other cohorts[25] have demonstrated the importance of primary renal disease in progression of CKD. Our analysis suggests that the cause of CKD may also have bearing on the risk for AKI. It is of interest that, in line with evidence that patients with ADPKD have been shown to have more rapid rates of eGFR loss[26,27] than other causes of CKD, here we have demonstrated that they also appear to be at increased risk for severe AKI episodes. It may be that these two findings are mechanistically associated.

A key message from this study is that for each AKI episode suffered by a patient, there is an increasing likelihood that the next AKI will be more severe and be stage 2 or 3 rather than stage 1. Furthermore, these more severe AKI are associated with an escalating risk for progression to RRT. If a second AKI is stage 2 or 3 (rather than

stage 1), the patient has a 14 fold increased risk of reaching ESRD. If a third AKI is stage 2 or 3, the risk of reaching ESRD is 28 fold. Whilst speculative we would propose that recurrent episodes of AKI lead to progressive fibrosis or low-grade inflammation of the kidney could be responsible for this progression to ESRD. Episodic AKI appears to be linked to progression of CKD, regardless of the cause of the AKI."

AKI episodes were not associated with an increased risk for long-term mortality. This is in contrast with the findings of previous studies.[13,28–30] This difference may relate to the fact that previous investigations have considered patients with more preserved baseline levels of renal function. The uraemic milieu of advanced CKD is a potent competing risk factor that may attenuate the mortality risk otherwise associated with AKI.

5.7 Limitations

This study has limitations that should be carefully considered. Although care was taken to validate AKI events, the aetiology of each AKI episode was not considered. It is therefore likely that different causes of AKI will have different natural histories, pathogenic effects within the kidneys and systemic outcomes. AKI was defined by the KDIGO definition through analysis of serial serum creatinine measurements without corroborative information on urine output. The AKI episodes were retrospectively identified and not totally in hospitalization and therefore the definition of AKI by KDIGO guideline is not fulfilled of the 7-day period limit. It is also possible that patients who live furthest from our Hospital site may have admissions to other hospitals for AKI management and follow up but for which we did not capture laboratory data. This is likely to explain the association between geographical location and AKI risk. We have also assumed linearity in the rate of decline in renal function. This assumption is not always correct, especially in the period preceding initiation of RRT. [6,31]

Due to the referred nature of the study population, in a hub and spoke model of delivery of renal specialist care, almost 20% of the population had an immune mediated cause for their primary kidney disease (i.e. glomerulonephritis or

vasculitis). Although patients with a background of for example ANCA-associated vasculitis can suffer pre-renal AKI, there is also the possibility for flares of intrinsic renal disease to occur. It may therefore be that the quantified risk detailed here cannot be directly applied to a general population CKD cohort that are not cared for in a specialist centre, although we expect the same principal of sequentially increasing risk associated with each AKI suffered by a patient to apply.

For the purpose of analysis, we assumed that in patients who had no AKI events, all repeated measurements contributed to the period prior to a first AKI. It is possible that a small number of these latter observations may have belonged to the period one month prior to an, as yet unobserved, AKI. Previous sensitivity analysis, however, suggests that the impact of this would be negligible. Analysis was unable to include baseline CKD at study entry in the statistical model, due to the heterogeneity of geographical origin and laboratory results which could be influential on the results. However the model does point to AKI being a predictor in CKD progression, future AKI and mortality independent of baseline eGFR given that the latter is in the statistical model.

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Chapter 6

Reducing acute kidney injury incidence and progression in a large teaching hospital

6.1 Rationale

This chapter is the main interventional study of this thesis. It details a Trust wide acute kidney injury (AKI) quality improvement project. Background work from this PhD in chapters 1, 3, 4 and 5 detailed the importance of this work and informed some of the later iterations of the PDSA (plan, do, study, act) cycles, the change package and the maintenance phase.

This work has been published in BMJ Open Quality, and presented at multiple events including the American Society of Nephrology in Chicago 2016 as well as being selected as a finalist in the national Quality improvement awards in Leicester in 2017.

BMJ Open Quality DOI: 10.1136/bmjoq-2017-000308

6.2 Abstract

Acute kidney injury (AKI) is a common syndrome that is associated with significant mortality and cost. The Quality Improvement AKI Collaborative at Salford Royal Foundation Trust (SRFT) was established to review and improve both the recognition and management of AKI. This was a whole-system intervention to tackle AKI implemented as an alternative to employing separate AKI nurses. Our aims were to reduce the overall incidence of AKI by 10%, to reduce hospital acquired AKI by 25%, and to reduce the progression of AKI from stage 1 to stage 2 or 3 by 50%.

From 2014 to 2016, several multifaceted changes were introduced. These included system changes, such as inserting an e-alert for AKI into the electronic patient record, an online educational package and face-to-face teaching for AKI, and AKI addition to daily safety huddles. On ten Collaborative wards, development of an AKI care bundle via multidisciplinary team PDSA (plan, do, study, act) testing occurred.

Results showed a 15.6% reduction in hospital-wide acquired AKI, with a 22.3% reduction on the collaborative wards. Trust wide rates of progression of AKI 1 to AKI 2 or 3, showed normal variation, whereas there was a 48.5% reduction in AKI progression on the Collaborative wards. This implies that e-alerts were ineffective in isolation. The Collaborative wards' results were a product of the educational support, bundle and heightened awareness of AKI.

A number of acute hospitals have demonstrated impactful successes in AKI reduction centred on a dedicated AKI nurse model plus e-alerting with supporting changes. This project adds value by highlighting another approach that does not require a new post with attendant rolling costs and risks. We believe that our approach increased our efficacy in acute care in our front-line teams by concentrating on embedding improved recognition and actions across the MDT.

6.3 Problem

Acute kidney injury (AKI) is a common and serious syndrome affecting patients both in hospital and in the community.[1] It is associated with significant morbidity and mortality. Recognition and management of AKI in the UK has been described as poor over the last decade by the NCEPOD report 'Adding insult to injury'.[2]

This study was designed to evaluate methods of reducing the incidence and progression of AKI through multi-faceted interventions, and to evaluate the impact of these on AKI incidence, AKI progression, in-hospital length of stay, and mortality.

We used the Institute for Healthcare Improvement's Breakthrough Series Collaborative Model methodology.[3] The AKI collaborative agreed three main aims:

- reduce the overall incidence of AKI by 10%,
- reduce the incidence of hospital acquired AKI by 25%

- reduce the progression of AKI from stage 1 to AKI stage 2 or 3 by 50%

The population and demographics of Salford are described in the generic methods chapter. The Trust is one of the most digitally mature Trusts in the NHS and, as such, the electronic patient record (EPR) system lends itself to large, anonymous data collection and analysis.

SRFT centres around Quality as its operating principle with a strategy supported by a Quality Improvement (QI) department since 2007 delivering change through collaboratives, microsystems, clinical quality academies, lean and flow interventions.

6.4 Background

AKI has a reported incidence of 12 - 17.7% from recent UK studies and it affects a wide range of patients both in hospital and the community. It occurs across a wide range of specialties, with most episodes of AKI occurring and being managed independent of nephrologists.[7] AKI is associated with longer lengths of hospital in-patient stay and has been associated with over 40,000 deaths per annum in the United Kingdom.[5] The cost of treating AKI is estimated at over £1 billion per year, which is 1% of the annual NHS budget.[5]

AKI is associated with poorer long-term renal outcomes for patients. A large cohort study from Sweden showed higher incidence of chronic kidney disease at one year in patients who have had an AKI compared to patients without (6% vs. 0.44%), and the incidence of end stage renal disease at five years was also higher (3.9% vs. 0.3%).[8] Recovery after AKI varies significantly, but over 40% (n=46) of *de novo* AKI failed to recover back to baseline in patients without pre-existing renal impairment in a small, single centre study. [9]

AKI came to the forefront of the UK national agenda following the national confidential enquiry into patient outcomes and death (NCEPOD) report of 2009 'Adding insult to injury'. This landmark enquiry highlighted global failings in recognition and management of AKI and showed that only 50% of care was considered good.[2]

There have been two recent QI studies, by Central Manchester NHS Foundation Trust (CMFT, now part of Manchester University NHS Foundation Trust) and by

Liverpool hospitals that have attempted to tackle this problem. Each have employed the use of AKI nurses, AKI education, AKI bundles, and AKI e-alerts.[10,11]

CMFT employed two AKI nurses to screen their highly sensitive AKI e-alerts and to ensure their ten-point AKI priority care checklist was being completed. Alongside previous didactic teaching sessions, they developed novel opportunistic teaching with a 4 slide micro teaching package. This generated a 28% reduction in AKI incidence, a 23% reduction in AKI-related length of stay, and a trend towards improved mortality.[10]

The Liverpool hospitals took a similar approach, consisting of education, e-alert, bundle and a dedicated outreach team. This generated a 23.2% reduction in in-hospital mortality, a 25.9% reduction in 30-day mortality, and a 2.6-day improvement in length of stay.[11]

The AKI Steering group and senior sponsors recognised the majority of AKI occurs outside of the renal ward.[7] AKI can be seen as an 'illness barometer' that reflects the underlying severity of illness of the patient. Therefore, this project purposefully did not appoint AKI nurses, and instead aimed to change Trust-wide culture through interventions that share recognition of, responsibility for, and management of, AKI.

6.5 Measurement

6.5.1 Ethical considerations

As this was a QI study using anonymised data collection for both analysis and reporting, it is exempt from specific ethical approval.

6.5.2 Methods

The NHS England national detection algorithm[12] for AKI was programmed into our Telepath pathology system. Consequently, AKI results are automatically calculated in Telepath from available creatinine history. This in turn generates an electronic AKI flag that appears in the demographic banner of the EPR if sufficient deterioration in renal function is seen, according to the KDIGO (Kidney Disease, Improving Global Outcomes) definition of AKI.[13]

All pathology results are available in an SQL (structured query language) database.

The Information management and technology (IM&T) team were able to write a report to identify the data items needed for the indicators for the project. These data were pulled into Qlikview (Qlik, Pennsylvania, USA), a reporting tool that the group and the quality improvement team can access. In Qlikview, all the incident data about each AKI alert is provided. These data include the date of occurrence for each incident and ward on which the incident occurred. The number of patients with an AKI stage of either stage 1, 2 or 3 was recorded.

AKI alerts within 48 hours of hospital admission were deemed to be community-acquired as, within this time frame, it is likely that the insult that caused the AKI had occurred outside of hospital. AKI alerts that happened more than 48 hours after admission were classified as hospital acquired. The arbitrary use of 48 hours has been applied previously in other studies and provides a means by which community-acquired AKI can be broadly categorised and assessed independently of hospital acquired AKI. [14]

These data were downloaded from Qlikview every month and presented in statistical process control (SPC) charts to clearly display any statistical improvements as per the aims detailed above.

6.5.3 Collaborative

The QI project was based on the International Health Institute's Breakthrough Series collaborative model[3] and this model has been successfully used within the Trust previously in numerous other projects.

The SRFT AKI Collaborative Steering group was established in July 2014 in response to the recognition of AKI as a risk to patients and the rising profile of AKI on the patient safety agenda. A National Patient Safety Alert issued in 2014 mandated the introduction of a standardised computerised AKI detection algorithm.

The Collaborative steering group comprised QI facilitators, a clinical research fellow, pharmacists, practice educators, IM&T representatives, nursing representatives, and the pre-existing AKI working group (a self-selected group of interested consultants from Nephrology, acute medicine and intensive care). The steering group held a structured meeting every fortnight.

6.5.4 Baseline data

Baseline data were collected from November 2014 to August 2015. Pilot work, including an audit, had been undertaken in April 2014 to confirm the prevalence of AKI and the need for intervention. This showed that 212 patients were considered to have creatinine results indicative of AKI during that 1 month period. Of 177 AKI stage 1 events, 91 (51%) did not progress, 48 (27%) progressed to AKI 2, and 38 (21%) progressed to AKI 3.

6.6 Design

6.6.1 Learning sessions

Five learning sessions were used. Ten ward-based teams and one pharmacy team took part. PDSA testing was used in action periods supported by QI facilitation and steering committee member ward visits (Table 6-1).

The wards included (Table 6-2) were selected for their high incidence of AKI and diversity across medical and surgical specialities to better understand the different challenges faced in diverse environments. It was anticipated that this would then lead to a more universally applicable and effective change package.

Table 6-1. Learning sessions and dates

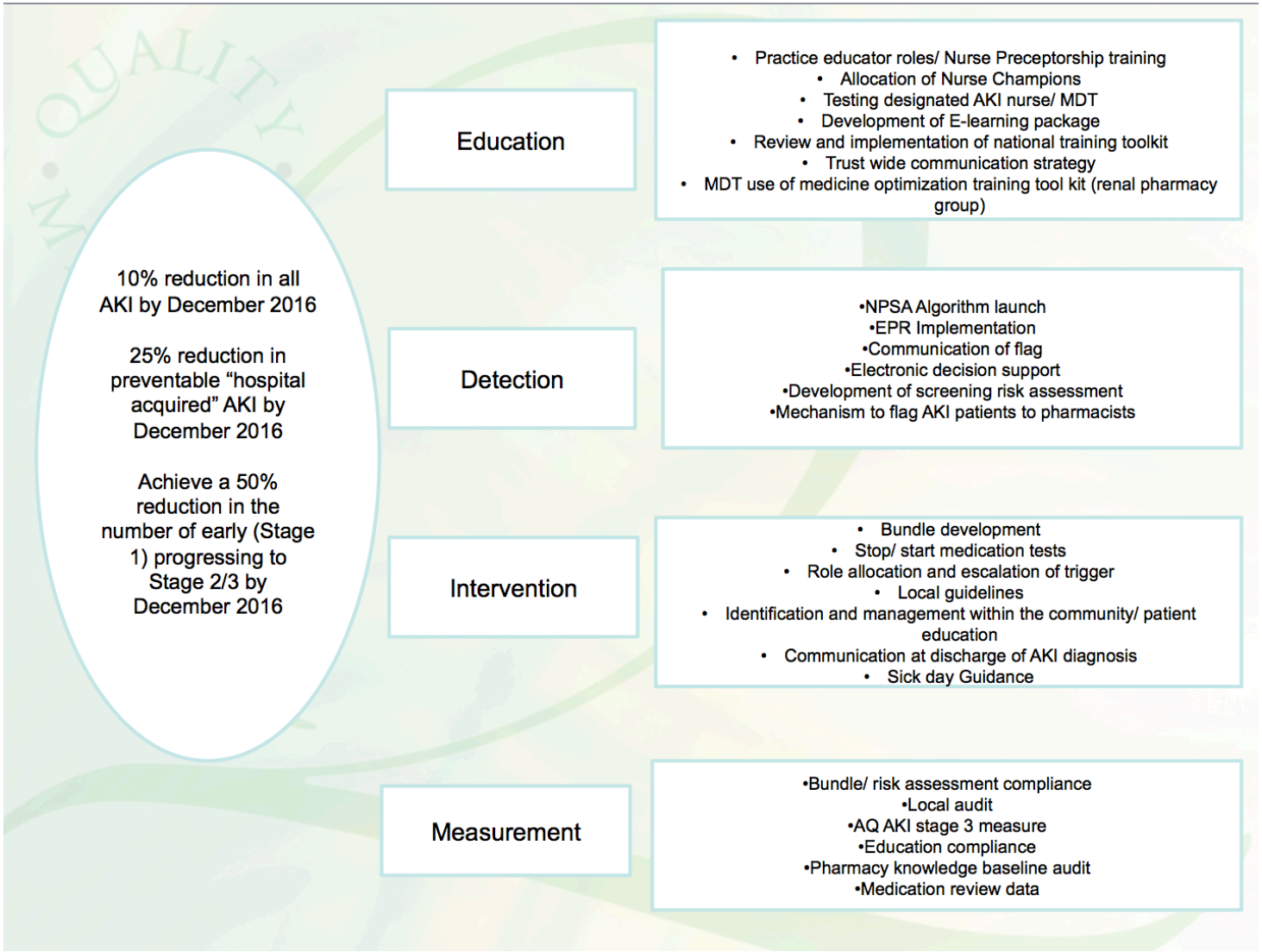
Learning Session 1:	17th August 2015
Learning Session 2:	10th November 2015
Learning Session 3:	10th March 2016
Learning Session 4:	8th June 2016
Learning Session 5:	3rd October 2016

Table 6-2. Ward abbreviation and specialty

Ward	Specialty
ANU	Acute neurology unit
B1	General surgical
B6	Orthopaedic/trauma ward
B8	Neurosurgery ward
EAU	Emergency assessment unit
H2	Respiratory ward
HCU	Heart care unit
L2	Gastroenterology ward
L5	Care of the elderly ward
SHDU	Surgical high dependency unit
Pharmacy team	

A driver diagram (shown in Figure 6-1) was developed. The aims were to reduced overall AKI incidence by 10%, reduce AKI progression by 25%, and reduce the incidence of hospital acquired AKI by 50% by December 2016. The interventions are detailed below.

Figure 6-1. Driver diagram to show the aims and work-streams for the AKI collaborative



6.6.2 AKI E-alerts

AKI is detected through a rise in serum creatinine according to the KDIGO guidelines.[13] This rise is translated into an alert if it meets the criteria within the national algorithm[12] in comparison to a previous creatinine result or presumed baseline. The national introduction of e-alerts became mandatory in 2015 in all Hospitals within the NHS.

E-alerts are a key intervention in the prompt recognition of AKI and careful consideration was given to the effective communication of the e-alert to the clinician through EPR. This was made more robust by a phone call from Biochemistry to the ward where the blood sample had been taken for every new AKI 3. Recent work with AKI in the local community has shown that e-alerts coupled with education leads to an improved response time.[15]

6.6.3 EPR documentation

A series of changes to the EPR documents were developed including the introduction of a separate AKI assessment and an AKI pharmacist assessment document. These were to be completed when a patient develops an AKI and linked to the AKI bundle. There is good evidence of the effectiveness of bundle use from the 'Surviving Sepsis' campaign. However, literature regarding bundle completion suggested that convincing clinicians to complete a separate document is challenging.[16,17]

Development of discharge advice for general practitioners to auto-populate on the discharge summary was also commenced. This was to be a safety net for patients whose AKI had not completely resolved on discharge to get re-referred to renal services or followed up in the community via the Primary Care CKD register, following the NICE CKD guidelines.[18] Potential challenges to this intervention were the need for strong communication links with primary care and the lack of evidence base for these recommendations that therefore left it open to challenge.

6.6.4 Education

A key component of the e-alert roll out was that it required supporting education and information. An e-learning package was developed and uploaded to 'Moodle', the Trust's host site for online learning. Here, there was a series of educational materials aimed at the multidisciplinary team to develop understanding of AKI, fluid balance, and the role of early intervention.

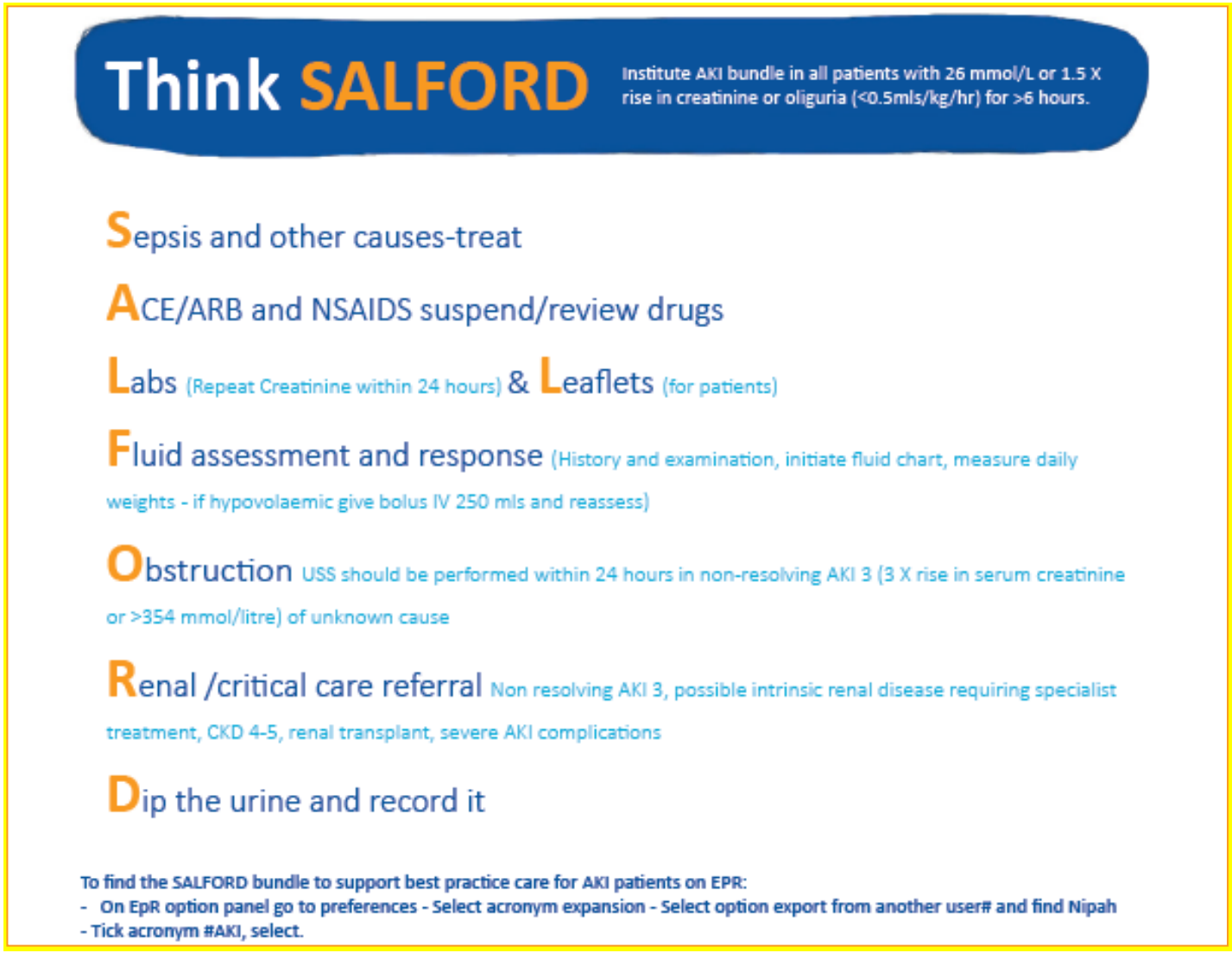
AKI education was introduced as a system change for healthcare assistant, nursing, and pharmacist induction. It was also provided at junior doctor induction and as part of formal compulsory protected curriculum teaching to the foundation, core medical, and acute care common stem medical trainees.

6.6.5 AKI bundle document

The Collaborative considered that the e-alert needed to trigger a tangible set of actions and interventions and provide clear advice to non-renal specialists about the referral pathway.

The renal consultants from the AKI working group developed the AKI bundle into an acronym – 'SALFORD' - in the hope that this would be easily memorable for those working at Salford Royal Foundation Trust (Figure 6-2). This bundle would then tie in with the EPR documentation and formulate the response to the trigger of an AKI e-alert.

Figure 6-2. AKI bundle poster



6.6.6 AKI care app

The AKI care app was developed in May 2015 and was designed in collaboration with the Greater Manchester, Lancashire, and South Cumbria Strategic Clinical Networks to be a free, user-friendly and simple app to help guide management for AKI. It is based on the previously described detection for AKI using the national algorithm and the investigation and management of AKI using the framework of the acronym 'SALFORD' for the AKI bundle.[19] This is discussed further in Chapter 7.

6.6.7 Pharmacy intervention

As part of the bundle, and as an intervention in its own right, the pharmacy team planned to do a medicines reconciliation on every patient with a new AKI. An AKI medicines reconciliation pro forma was integrated into EPR. The pharmacy team and the renal physicians in the Collaborative agreed the categories that pharmacists should review. An internal aim was made that pharmacists would attempt to review medications within 24 hours of the AKI e-alert. The pharmacy team also noted which member of the parent medical team they had discussed any recommendations with.

6.6.8 Spread phase

Initially, the spread phase had been intended to be a three-phase approach with a further 10 wards incorporated into the scheme in June 2017, followed by a full Trust roll-out. Some of the interventions in the change package, such as integration into the 'safety huddle', e-alerts and AKI education are already being provided Trust-wide.

6.6.9 Sustainable

There were plans to make this sustainable from the outset. These included evaluating the successful interventions and testing these in a variety of environments, and agreeing dedicated pharmacist time to be allocated to medicines reconciliation from the outset. Education will be built into induction and teaching programmes for the entire multidisciplinary team, with both face-to-face teaching and online learning. In addition, the annual 'World Kidney Day' will be used as a prompt for AKI awareness.

6.7 Strategy

Five separate learning sessions were used to teach both the basics of AKI and quality improvement, and then to facilitate PDSA cycles with the 10 collaborative wards and pharmacy group. The PDSA cycles were designed to generate ward-specific small tests of change. These could be performed in individual real-world ward environments and then brought back to the group to discuss lessons, limitations and scope for adoption to other wards. The following section describes the individual topics and PDSA cycles undertaken within each.

6.7.1 AKI e-alerts

E-alerts appear as a red text alert with AKI stage and date of AKI stage entered into EPR in the patients' demographics banner. The AKI alert is updated if the AKI stage changes but the alert does not disappear, to remind the clinician that patient remains at risk of AKI.

Some feedback was given regarding the alert remaining constantly red, and that this could be a significant cause of alert fatigue. There was also a period where the Critical Care Unit's laboratory data were not pulling through to the Qlikview, but this was recognised and rectified.

6.7.2 Safety huddle

Each day, nurses on each ward have a safety huddle that occurs at the changeover of shifts that include details of important safety concerns for individual patients.

PDSA 1: trialled highlighting patients with AKI and indicating AKI stage.

PDSA 2: added any outstanding aspects of the AKI bundle.

This was felt to be helpful and this intervention generated discussion with the responsible clinician, anecdotally improving communication around AKI. There are challenges, as the e-alert does not disappear when the AKI has resolved: this requires a manual trawl by the nurse in charge of the patient of the creatinine results and AKI stage to update the handover list.

6.7.3 AKI bundle (Figure 6-2)

Each section of the AKI bundle required individual attention and is described below.

PDSA 1: conception of the bundle and the acronym 'SALFORD', development of

bundle and badge sized ‘business cards’ with the acronym on.

PDSA 2: there was little interest in, or use of, the cards - however, the acronym became embedded in EPR.

There was poor engagement with completing the bundle documentation. Feedback focus groups stated that the form was not user-friendly, not intuitive, and appeared to be designed for audit purposes rather than improving AKI care.

6.7.3.1 Sepsis and other causes of AKI

This part of the bundle was incorporated into a program of education to identify and manage AKI. This is described in more detail in section 6.4.

6.7.3.2 ACE-I / ARB, ‘nephrotoxic’ or ‘volume toxic’ medications

The pharmacy team took ownership for the medicines reconciliation proforma and auditing their own performance. Alongside this, educational material and case studies were included in the medical staff education work stream.

PDSA 1: development of medicines reconciliation pro forma to document recommendations, and which junior doctor this was discussed with.

Audit of this work after cycle 1 showed that 76% of patients were reviewed within 24 hours and over 90% of patients had recommendations for medication dose adjustments and 80% had a medication that was recommended to be suspended. 63% were taking at least one volume toxic or nephrotoxic medication. 95% of recommendations made by the pharmacy team were adhered to.[20]

PDSA 2: aimed to improve medicines reconciliation review to within 24 hours of new AKI Monday to Friday.

Unexpected benefits in this area were that the pharmacy team became their own monitors and performance regulators. They dedicated time for AKI medicines reviews, and act as a human reminder for e-alerts to medical staff by documenting with whom they have discussed the medicines recommendations.

6.3.7.3 Labs and leaflet

This part of the bundle was aimed at ensuring that appropriate follow up monitoring of creatinine (labs) was performed and that patient information was provided (leaflets). The need for a repeat creatinine was conveyed through education.

PDSA: A basic patient information leaflet for AKI

There were several issues with the patient information leaflet, such as determining who had the responsibility to give it to the patient and who was responsible for accompanying information such as sick day guidance or fluid guidance. The documentation of either of the above was dismal.

The reading age and language in the patient information leaflet was pitched too high for widespread comprehension. As a result, new leaflets are being developed with the help of a patient advisory group, and a short video is currently under development.

6.3.7.4 Fluid balance

PDSA 1: Health care and nursing staff formally signed over responsibility of appropriate fluid balance monitoring for AKI patients from outgoing to incoming staff during safety huddles.

Specific education at induction and a healthcare specific Moodle learning resource and quiz were developed.

6.3.7.5 Obstruction

Education sessions included reminders to doctors and nursing staff that up to 5% of AKIs are caused by obstruction, and that bladder scanning or ultrasound imaging of the upper urinary tract should be considered. Ultrasound scans within 24 hours are indicated for a patient with an AKI 3 and no other obvious cause.

6.3.7.6 Renal / critical care referral

The reasons for referral were agreed by the nephrology consultants in the steering group: non-resolving AKI 3; possible intrinsic renal disease; AKI in patients with pre-existing CKD stages 4 or 5; AKI in transplant patients; severe AKI complications. Education regarding when patients should be referred to renal services were conveyed through education.

6.3.7.7 Dipsticks

Education was targeted at health care assistants and nurses performing and documenting fluid balance and urine dipsticks. A trial of performing urine dipstick on all patients admitted to the Medical Admissions Unit, regardless of AKI, was

discontinued over concerns of an increase in inappropriate antibiotic prescriptions with minimal other changes in management.

6.7.4 Education –Moodle and formal teaching

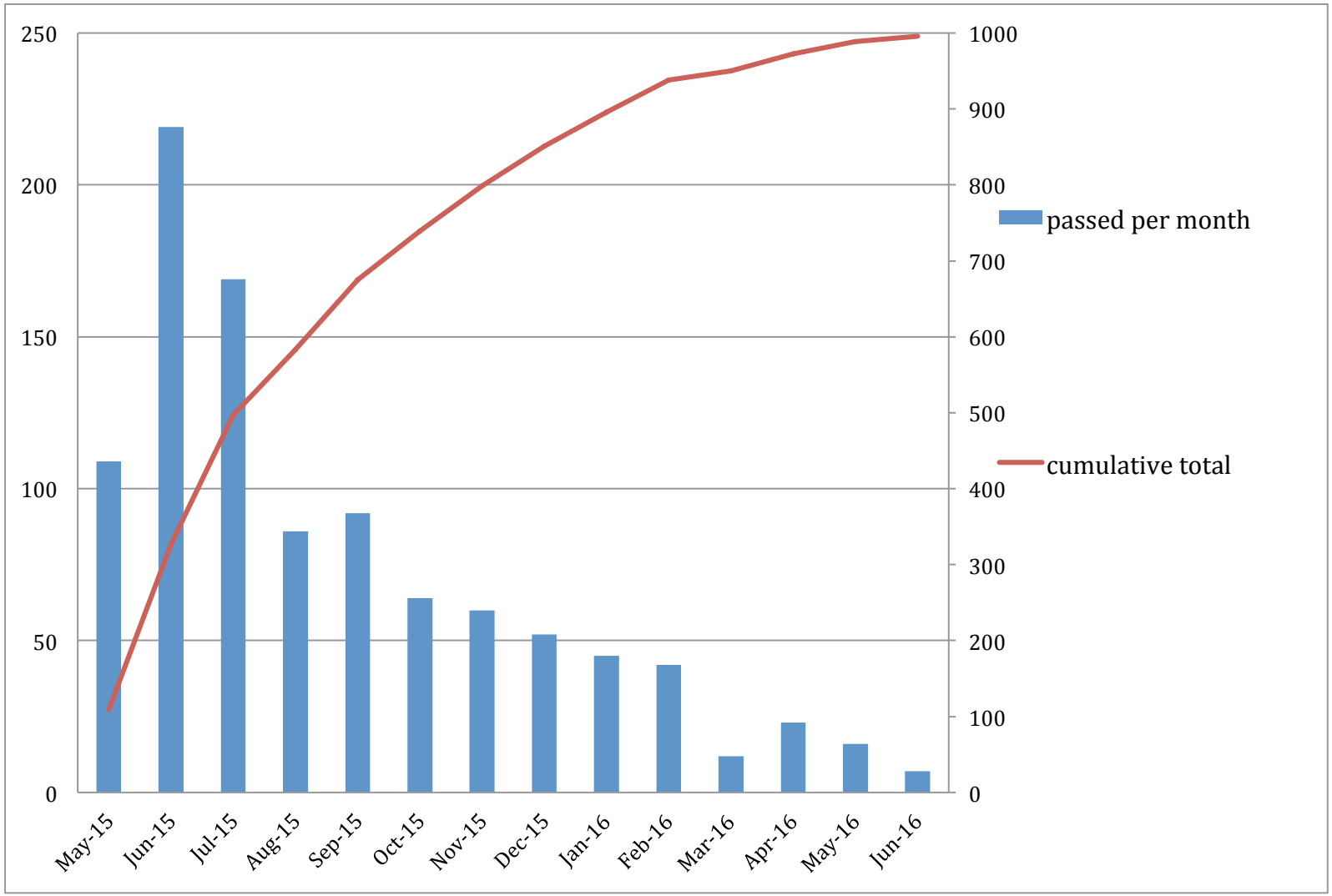
A substantial programme of education was undertaken across the Trust site. This was developed in conjunction with the Trust learning and development team. Teaching events were undertaken at induction, foundation and core medical training compulsory curriculum education sessions, and for emergency village staff (doctors, nurses, advanced nurse practitioners). Online versions of these were also available, and an accompanying online quiz to test knowledge was successfully completed by over 1000 employees by December 2016 (Figure 6-3).

PDSA 1: introduction of online learning

PDSA 2: engagement of nurse champions, some ward matrons supported the learning by withholding off-duty until staff nurses had completed it.

PDSA 3: AKI learning now part of mandatory induction for all staff. Foundation and core medical trainees also now have annual face-to-face education sessions via case-based discussion.

Figure 6-3. Number of individuals at the Trust passing the moodle AKI skills quiz by month



6.7.5 Badges, stickers, information boxes

Different wards decided to create different ways of highlighting or managing patients with AKI. They developed magnetic badges for the patient allocation board, the boards behind each patient bed. They also created brightly coloured filing boxes to keep together AKI-related items such as printed information like the bundle assessments, fluid balance sheets and the patient information leaflets. These were of variable success because of staff rotation, so routine use of this strategy was abandoned.

6.7.6 AKI nurse champions

PDSA 1: Volunteer/nominated nurse champions attended learning sessions on behalf of their wards. They underwent additional training from the QI team and the learning and development team to gain more knowledge about AKI, QI theory and support in relaying this back to their base ward.

This QI project has taken place during a period of unprecedented demand on the NHS and staffing. Recruitment and retainment are issues affecting all areas of the Trust, and, as a result it has been especially difficult to get both regular and reliable attendance by named individuals at these organised learning sessions. Despite email reminders to both individuals and ward managers and physical walk rounds to ensure attendance, it has been increasingly difficult to maintain a turnout.

PDSA 2: The learning sessions were reduced from full day to half day or shorter sessions.

6.7.7 Junior doctor AKI champions

PDSA 1: A select group of self-declared interested foundation doctors.

Owing to four-monthly job rotations this was significantly less effective as an intervention than anticipated. The improvement work was also not fully supported from all wards, with poor buy-in from some senior clinicians. This created a significant barrier to supporting doctors or nurses working as AKI champions within these environments.

6.7.8 Electronic patient record (EPR) AKI documentation

Several changes to the EPR were made.

PDSA 1: AKI assessment and AKI pharmacy assessment documents.

PDSA 2: An automated insertion on to the post-take ward round for AKI assessment.

PDSA 3: Discharge documents automatically alerted the need for AKI coding.

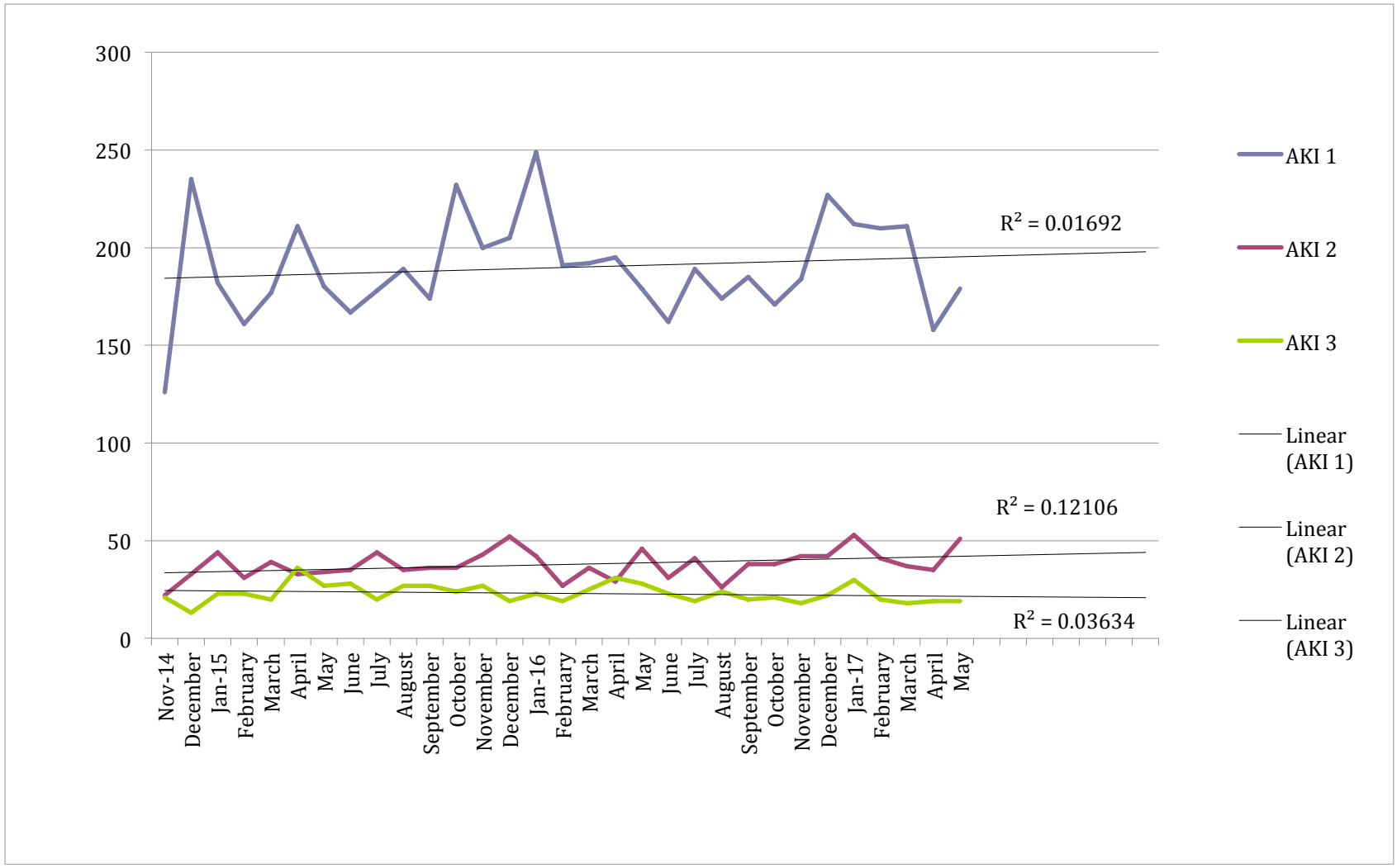
PDSA 4: An algorithm is being developed for automated advice on phlebotomy timing after discharge, based on stage and resolution of AKI.

An audit of completion of the AKI bundle document shows that use of the AKI document within 24 hours of first AKI e-alert by medical staff is at 1.9% (380 assessments completed for 19,699 AKI episodes). This clearly indicates that the AKI document itself is not responsible for the improvements seen.

6.8 Results

Over the course of the Collaborative work there was a trend towards an increase in total episodes of AKI, in particular AKI stage 1 (Figure 6-4). These data remained within the limits of normal variation, with an average incidence of 277 AKI episodes per month.

Figure 6-4. Number of episodes of AKI by stage per month



Trust-wide, there was a decrease in hospital acquired AKI of 16% compared to baseline (Figures 6-5 and 6-6). When reviewing the data for the Collaborative wards separately (Figure 6-7), the results are more pronounced: a 22% decrease in episodes of hospital acquired AKI compared to baseline.

A review of the AKI progression (Figure 6-8) shows monthly trends in the number of Trust-wide episodes of AKI Stage 1 progressing to either AKI Stage 2 or 3, at least 48 hours after admission. There was no impact on the overall net incidence of AKI progression. However, when the data for the Collaborative wards (Figure 6-9) were analysed independently, the number of stage AKI Stage 1 events that progressed to either AKI Stage 2 or 3 reduced by 48% in comparison to baseline.

This suggests that the e-alert in isolation is ineffective at reducing AKI in this Trust. The reduction in hospital-acquired AKI and AKI progression seen on the Collaborative wards is correlated with the educational support, and the pharmacist and nurse champion work.

Both length of stay and dialysis incidence show a trend towards improvement, but, owing to the wide variation, it is likely that further longitudinal data points will need to be collected in order to demonstrate whether these are statistically significant (Figure 6-10). Mortality showed no significant change towards change (Figure 6-11).

Figure 6-5. Total number of AKI episodes across the trust during the study period. This SPC (statistical process control) chart shows normal variation

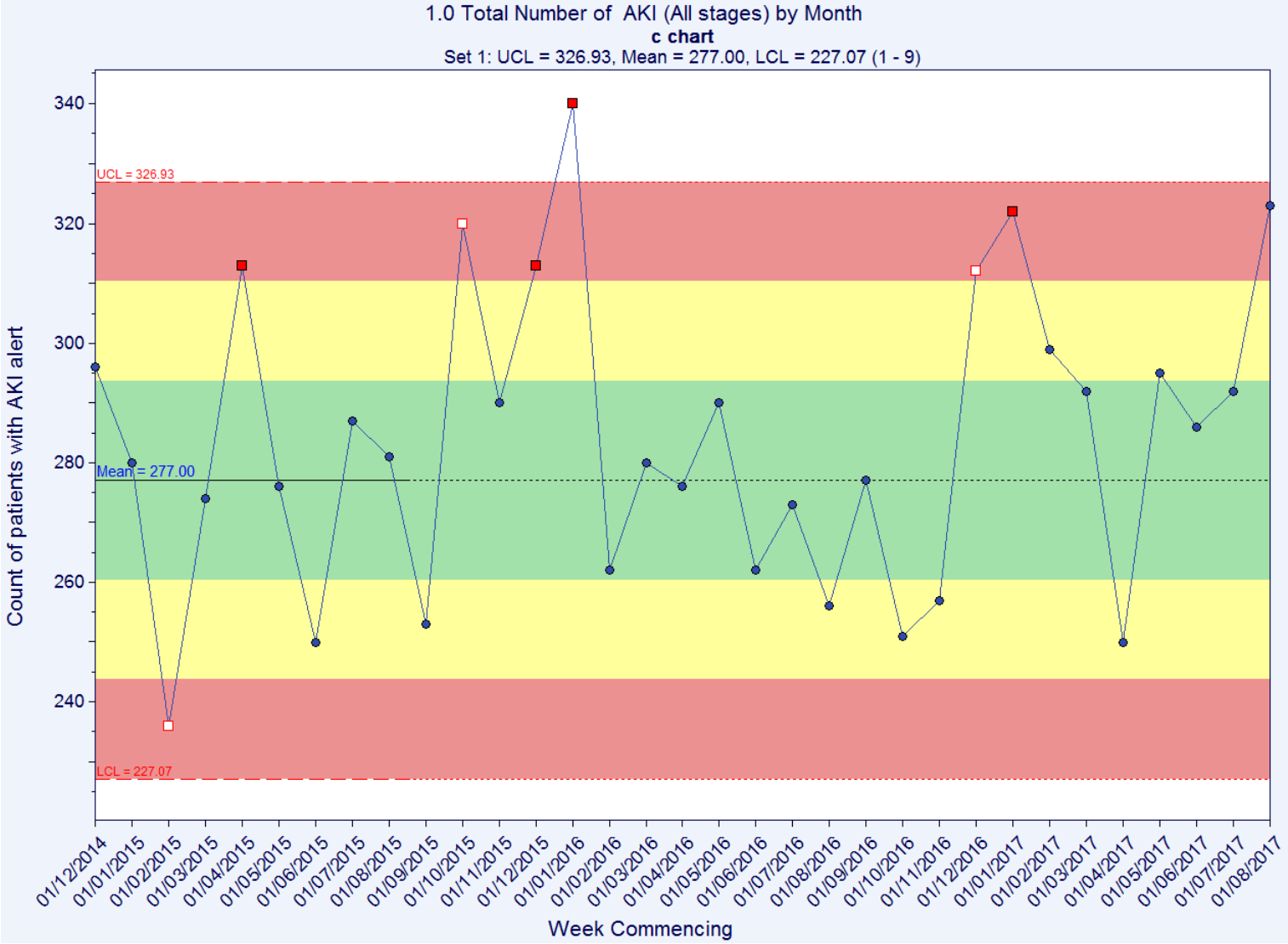


Figure 6-6. Number of episodes of hospital acquired AKI by month. This SPC chart shows a 16% reduction.

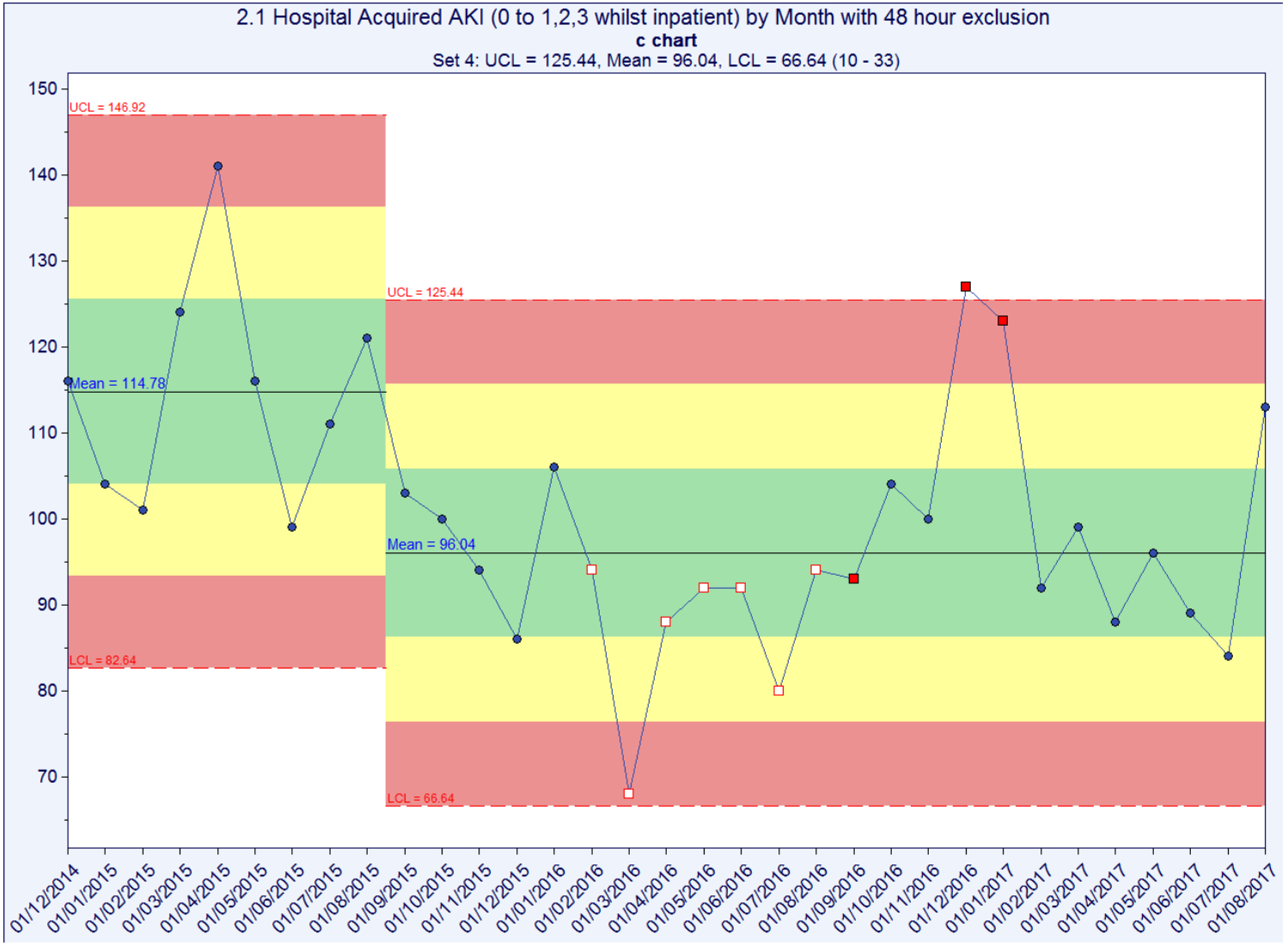


Figure 6-7. Number of episodes of hospital acquired AKI by month on the collaborative wards only. There was a 22% decrease in episodes of hospital acquired AKI compared to baseline.

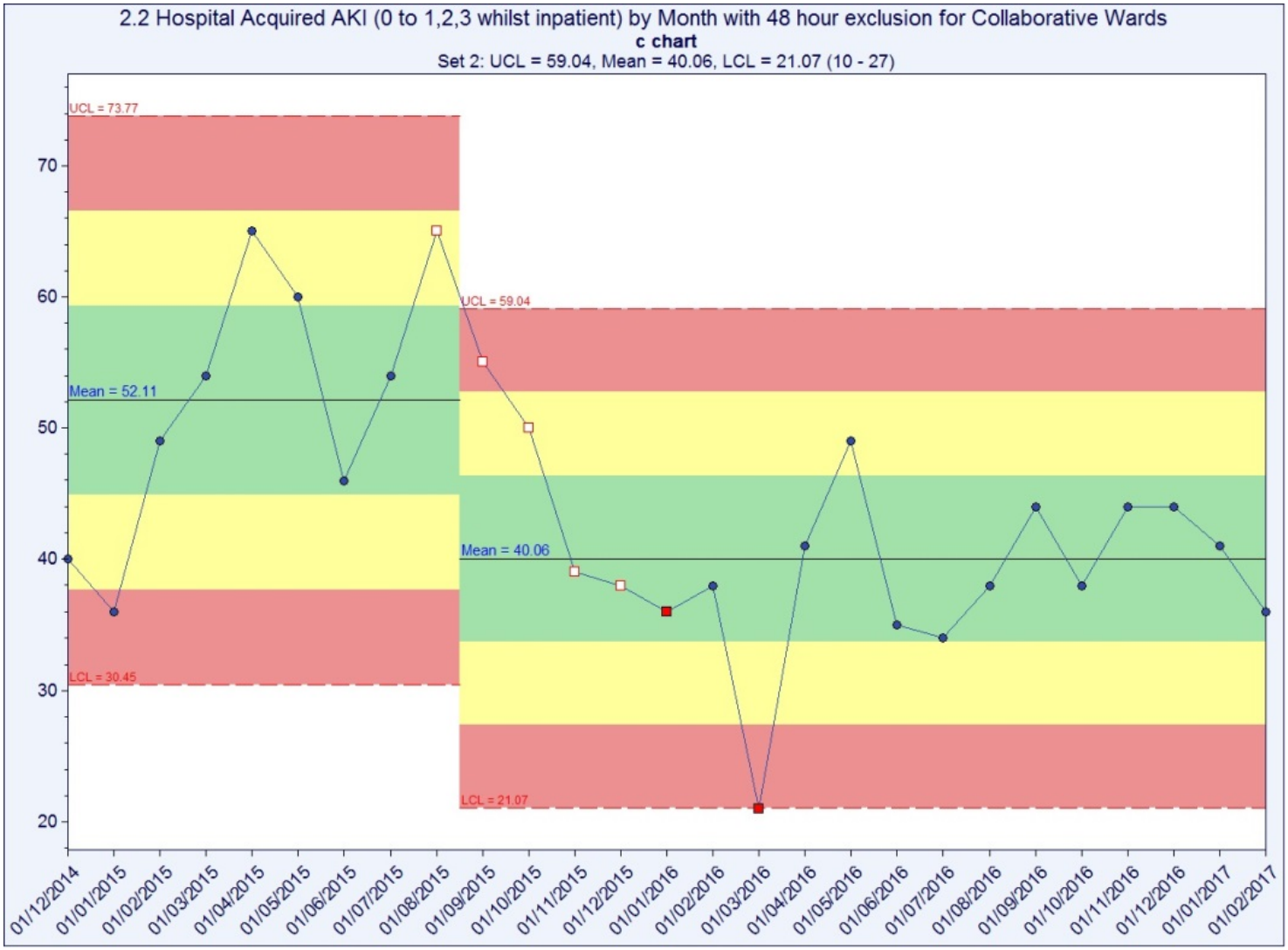


Figure 6-8. Number of AKI stage 1 progressing to either AKI stage 2 or 3, 48 hours after admission, by month. This figure shows normal variation.

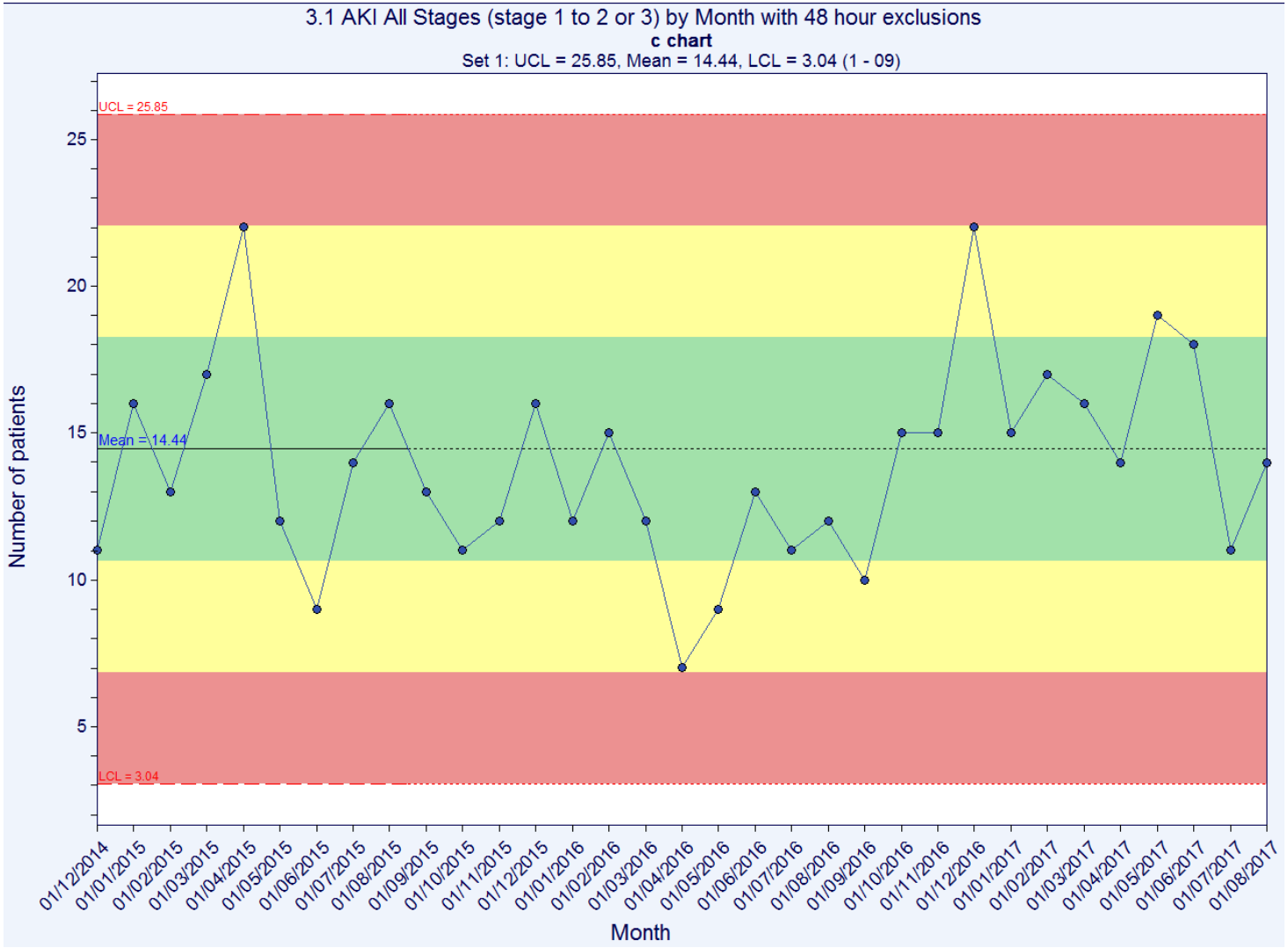


Figure 6-9. Number of AKI stage 1s progressing to either AKI stage 2 or 3 on the collaborative wards only, 48 hours after admission, by month This shows a 48% reduction in episodes on the collaborative wards in comparison to baseline.

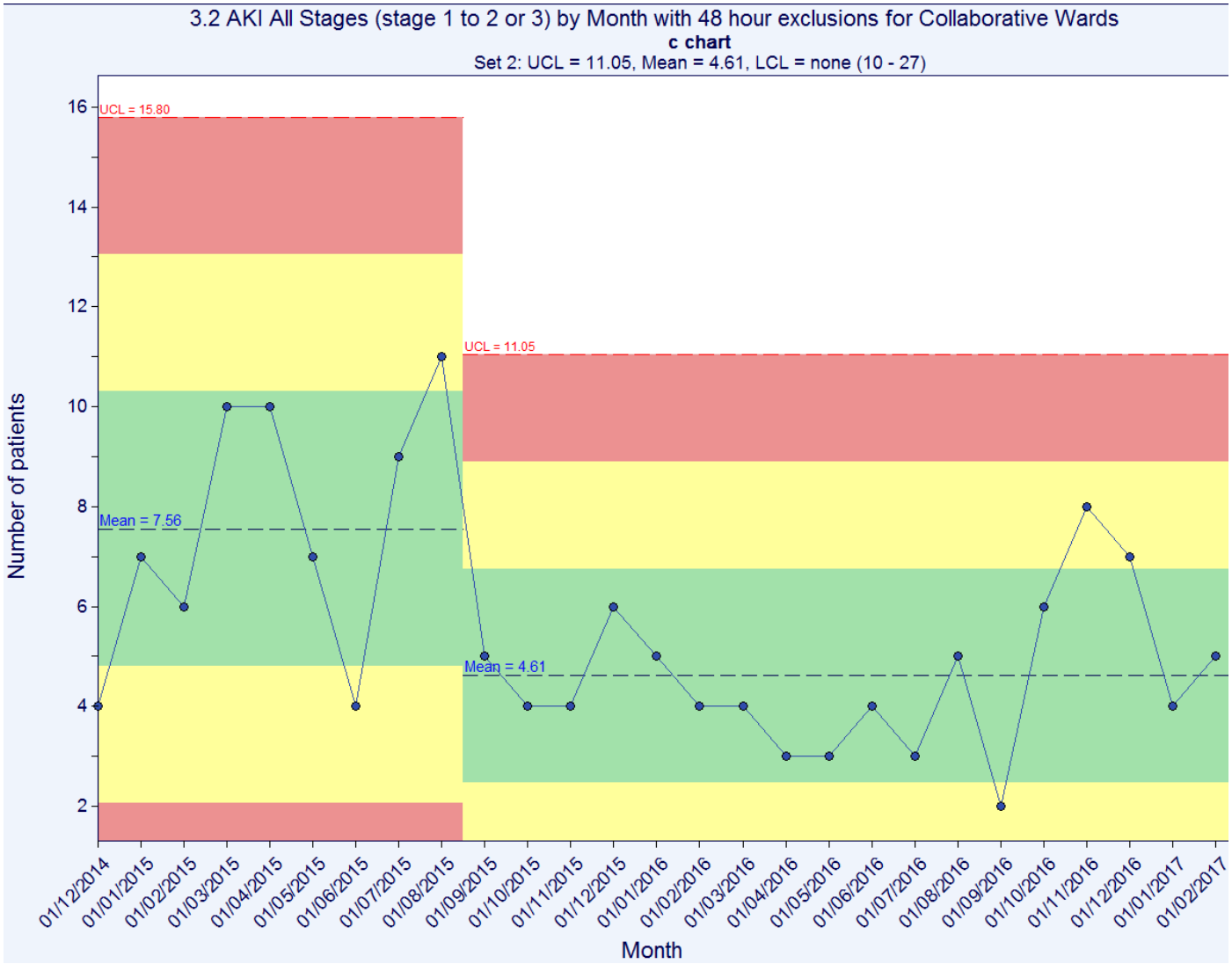


Figure 6-10. The mean length of stay and the dialysis incidence per month. Both show a trend towards improvement.

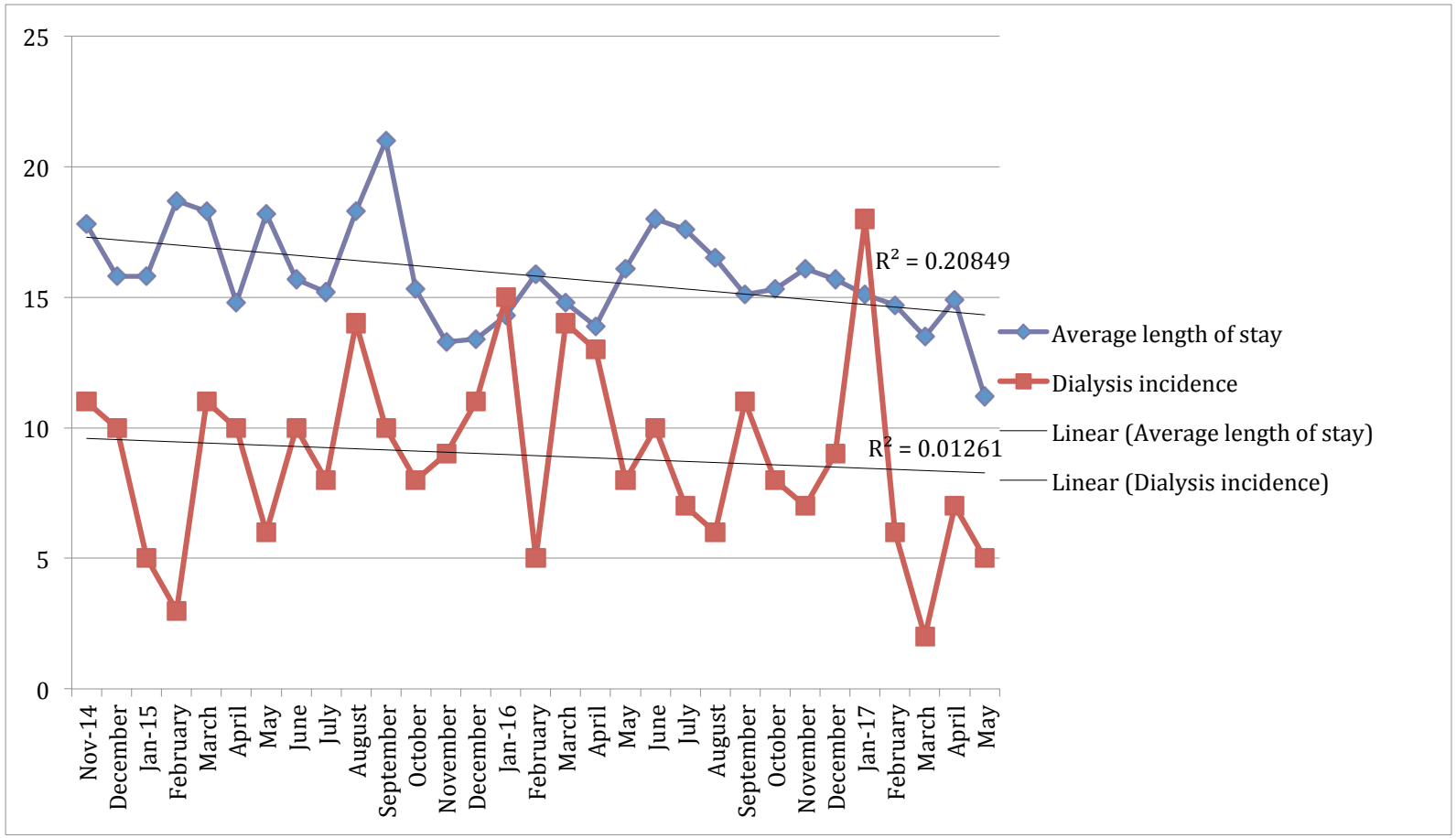
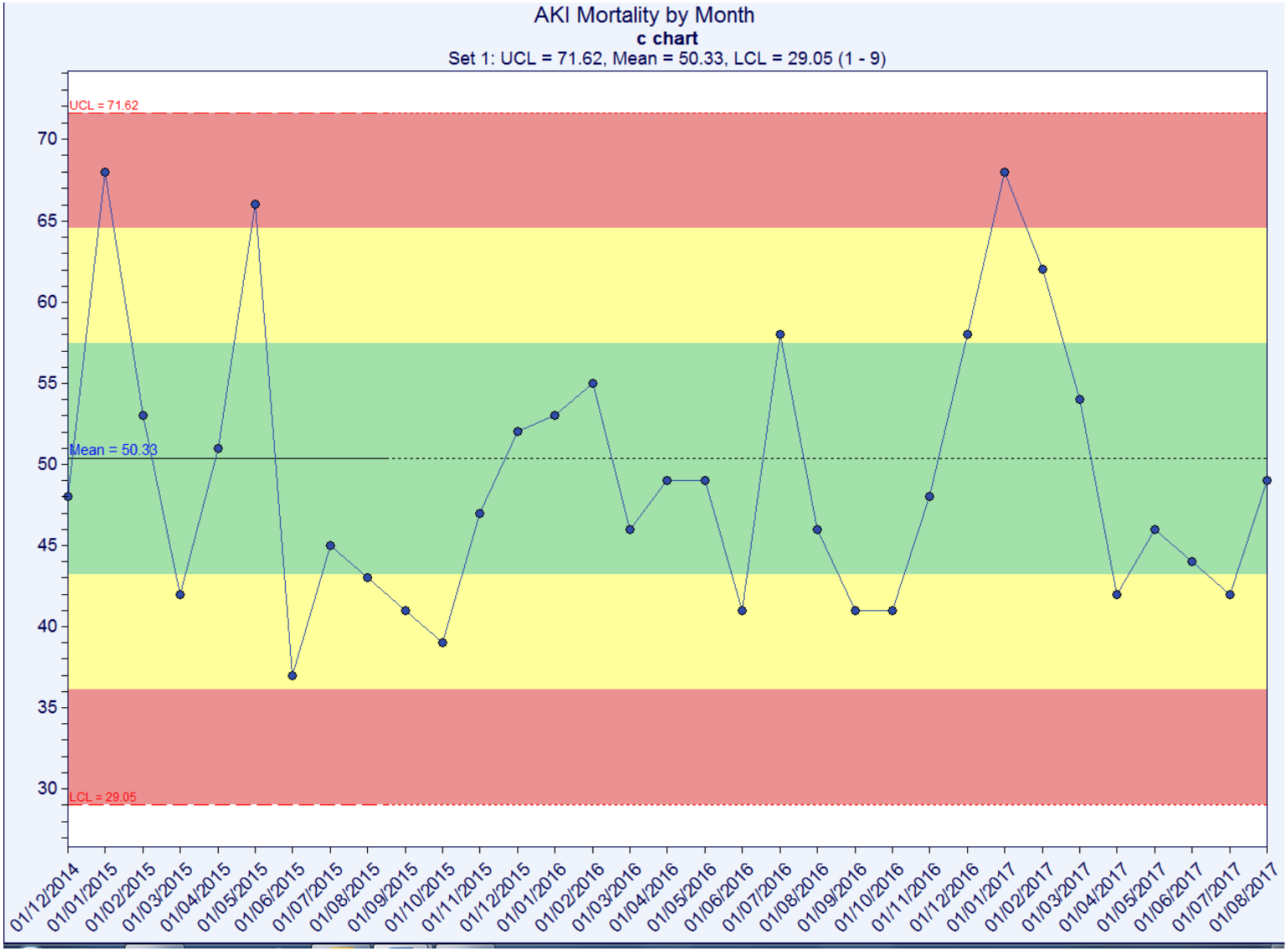


Figure 6-11. The average mortality of patients with AKI per month



6.9 Lessons and limitations

There were some limitations that are both system-wide and NHS-wide. The pressures on staffing which affected the numbers of staff released to attend learning sessions, coupled with high staff turnover, impacted on the consistency and therefore knowledge base of staff present at each learning session.

We learned that it was key to have a backbone of QI staff to organise the learning sessions, teach and facilitate QI methodology and corral input. Over the course of the project there was reduction in frequency of meetings of the AKI working group from fortnightly to monthly and these were increasingly poorly attended. Exploration of alternative meeting times, which were no longer out of hours, was met with resistance or apathy.

There was a disappointing reception from junior doctors with regard to becoming involved in the tests of change, to bundle acceptance and completion.

Such a large and complex QI project does not lend itself easily to detailed record keeping regarding PDSA cycles and exact timings. Future projects would plan meticulous minutes taking during meetings with support of audio recording or dedicated typist and date/time stamping of activities to enable accurate evaluation.

6.9.1 Strengths

There were several strengths in this project, not least the outcomes, which were statistically significant. This could not have been achieved without the stability of the QI staff support that was invaluable in arranging meetings, setting and making notes on agendas, data handling and the synthesis of the change package. The facilitation and experience of the QI staff allowed the project to run smoothly and freed up other members of the collaborative from the administrative and organisational jobs necessary for this project.

Other strengths were the engagement from the pharmacy and nursing teams, as both of these were early adopters of change. The incorporation of the AKI alert into the nursing safety huddle and the pharmacy medicines reconciliation both act as a redundancy in the system for the e-alert for AKI. These are also two separate opportunities to engage with clinicians to alter management for patients and serve to make the system of recognition of AKI and its subsequent management more robust.

The whole system approach to change has resulted in the opportunity to upskill the frontline multidisciplinary team not only in AKI but also the deteriorating patient and sepsis.

6.9.2 Generalisability

The principles of this AKI project are of a change in culture, which is low cost, easily replicated, and generally applicable to all care settings. Large portions of AKI recognition tie in with other key initiatives such as early recognition of the deteriorating patient.

As many hospitals have similar nursing, pharmacy and IM&T support to SRFT, this culture change would require minimal additional expenditure. Expenditure is required for dedicated pharmacy review time, for educational training, and for IT support.

Educational packages can be made universal and also be made part of the medical student curriculum as a separate module.

6.10 Conclusion

One of the biggest practical challenges will occur as the QI team step back from the project, as this will leave a void in organisational and practical support and other members of the working group will need to step into these roles. In order to make this project robust and sustainable there will need to be a focus in coming months on generating appropriate redundancies in the system to ensure that the statistical improvements are sustained.

Work is left to be done in the community and looking at secondary prevention as, to date, we have made no impact no incidence of community acquired AKI overall. This is likely to be because the majority of interventions are based on reactionary measures in response to e-alerts rather than risk prediction or joining forces with review of the deteriorating patient initiatives.

A number of acute hospitals have now demonstrated impactful successes in AKI reduction using traditional service improvement and QI methodologies. Almost all appear to have centred on a dedicated AKI nurse model plus e-alerting with supporting changes. This project adds value by highlighting another approach that

does not require a new post with resultant rolling costs and risks. We believe that as our approach concentrated on embedding improved recognition and actions across the MDT, it has had the benefit of having increased our efficacy in acute care in our front-line teams.

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Salford Royal NHS Foundation Trust AKI collaborative team

Rob Nipah (Acute medical consultant), Liam Doyle, Chedia Hoolickin and Lewis Edwards (Quality Improvement), Dimitrios Poulikakos, Janet Hegarty and Smeeta Sinha (Renal consultants), Lynne Sykes (Clinical Research Fellow), Elizabeth Lamerton (Pharmacy), Lynn Sterling (Learning and Development), Emma Flanagan (Information Management & Technology), Paul Johnston (Electronic Patient Records), Adam Brisley and Simon Bailey (Manchester University), Paul Ferris (Intensive care consultant), Gareth Byrne (Clinical Audit, Improving Quality data), Jill Carlin (Clinical director of radiology), Denise Darby (Pathology), Debra Lee (Lead nurse), Julie Newton (Lead nurse acute medicine), Gaynor White and Julie Winstanley (Emergency Admissions Unit).

Susan Howard, Delphine Corgie and Zoe Ashton (NIHR CLAHRC North West. The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC) Greater Manchester is a partnership between providers and commissioners from the NHS, industry, the third sector and the University of Manchester. We aim to improve the health of people in Greater Manchester and beyond through carrying out research and putting it into practice. http://clahrc-gm.nihr.ac.uk)

AKI care app developers, Greater Manchester, Lancashire and South Cumbria Strategic Clinical Networks, Rachel Challiner, James Ritchie

Chapter 7

The “AKI Care App”: live clinical decision support or reference tool?

7.1 Rationale

Chapter 7 discusses one of the strategies to reduce acute kidney injury progression and its complications. It details the working and user profiles behind the use of the “AKI app”. This app serves as a user-friendly Mobile application that can calculate AKI stage, help assess complications, and signpost the user to appropriate resources or for onward referrals. This app preceded widespread use of the AKI e-alert and was subsequently made obsolete by this and other in-hospital digital updates. It serves as a useful analysis of mobile applications and a reminder that technology development can rapidly become obsolete or outdated rapidly after being completely novel.

This work was presented at the European Renal Association, Madrid 2017 as an oral abstract. An abstract to this work has been published in NDT: “So044 The Introduction Of A Novel Smartphone App To Tackle Acute Kidney Injury In North West England” Sykes,L , Richie, J, May 2017, NDT 32(suppl_3):iii27-iii27, DOI 10.1093/ndt/gfx107.SO044

Nephrology, Dialysis, Transplantation DOI 10.1093/ndt/gfx107.SO044

Nephrology, Dialysis, Transplantation IPR policy: https://academic.oup.com/journals/pages/access_purchase/rights_and_permissions/publication_rights

7.2 Abstract

Background

AKI is common and associated with significant morbidity and mortality.[1] There is a need for rapid assessment, investigation and intervention to prevent progression and clinical deterioration. With smartphones now almost ubiquitous, there is the opportunity for point of care apps to provide clinical decision support for management of AKI. The AKI Care app was developed with this is mind. This study describes usage patterns of this app.

Methods

Anonymous clinical data entered into the app during live use were analysed. The user demographic details were noted for role, grade, clinical specialty, and geographical area of origin. Inputted values for pH, potassium, and creatinine were collated. The number and nature of any adverse features associated with AKI, and recorded via the app, were then analysed.

Results

AKI 3 was much more highly represented in the app than our usual hospital population (39.3% vs 15.0%). Of the 1428 creatinine entries, 38.5% were in increments of 100. The median pH (pH 7.18) and serum potassium (5.6mmol/L) were both outside the normal range. Complications of AKI were present in two thirds of the patients. These values and proportions would not be consistent with clinically expected results, and may represent inquiry or educational use.

Conclusion

The AKI Care app provides user-friendly technology for the any member of the multidisciplinary team to use at the point of care. But rather than being used for live decision-support, it appeared to be used as a reference and education tool. This suggests that clinical apps should pre-emptively include an educational component.

7.3. Background

AKI is a serious and common syndrome present in both the community and in hospital settings.[1] It is a rapid deterioration in the function of the kidneys that can lead to a multitude of problems, in particular electrolyte and fluid imbalance. AKI

can affect patients under the care of any clinical specialty. As such it is necessary to provide easy access to local and national guidelines for the investigation and management of AKI. There is a need for rapid assessment, investigations, and interventions in these patients to prevent AKI progression and clinical deterioration. The 2009 NCEPOD report Acute Kidney Injury: *Adding insult to injury*[2] highlighted that in the UK both AKI and its complications are poorly recognized and that investigations are often inadequate. The report concluded that 50% of care for all patients with AKI was substandard and up to 30% of deaths could have been avoided with the correct care.

Many initiatives to standardize the detection of and response to AKI were developed over the following years. These culminated in the mandated introduction of the AKI e-alert to all blood results in secondary care by NHS England in 2015.[3] This practice is now seen as the gold standard.

Clinicians caring for acutely unwell patients with changing physiology and symptoms may benefit from live management advice that is tailored to individual patients. The AKI Care app was developed as a free-to-download app with this is mind. The app was developed prior to the 2015 mandate of AKI e-alerts being introduced. As AKI occurs across such a wide range of specialties, it is difficult to maintain expertise in the detection, investigation and management of AKI across wards. The app was intended as a reference tool for different stages of AKI and their complications, and to provide signposts towards referrals to on-call renal or critical care teams as appropriate. It also includes links to Think Kidneys (‘NHS England. Think Kidneys National AKI programme. 2015'), the NICE AKI Guidelines (‘Acute kidney injury: prevention, detection and management) and the NICE Fluid Prescription Guidelines (‘Intravenous fluid therapy in adults in hospital) to support evidence-based learning.

After Apple’s App Store opened in July 2008 this allowed users to customize and download specific software applications or “apps” to their phone for the first time. With smartphones almost ubiquitous, an opportunity was seen to capitalize on this technology to create a point of care mobile app to guide investigation and management of AKI. There has been significant growth in the numbers of medicine-related apps, though those that have been downloaded and used repeatedly make up only a small proportion of the total.

Current literature describes the limitations of POC mobile apps in the UK due to their inability to integrate or communicate with other technology both in terms of alerts from the pathology spine, and also at the patient-clinician interface such as computers or workstations on wheels (COWs or WOWs). [7]

The aim of this study was to analyse and understand the use of this app in relation to clinical use.

7.4 Method

7.4.1 App development

The AKI Care app was collaboratively developed in May 2015 by renal teams in Greater Manchester, using a User Centred Design approach.[8] Development was funded by the Greater Manchester, Lancashire, and South Cumbria Strategic Clinical Networks. The Cheshire and Mersey AKI Network have supported subsequent software versioning via a funding grant from The North West Coast Strategic Clinical Network and Alexion Pharmaceuticals, however these grants and groups were not involved in this analytical study.

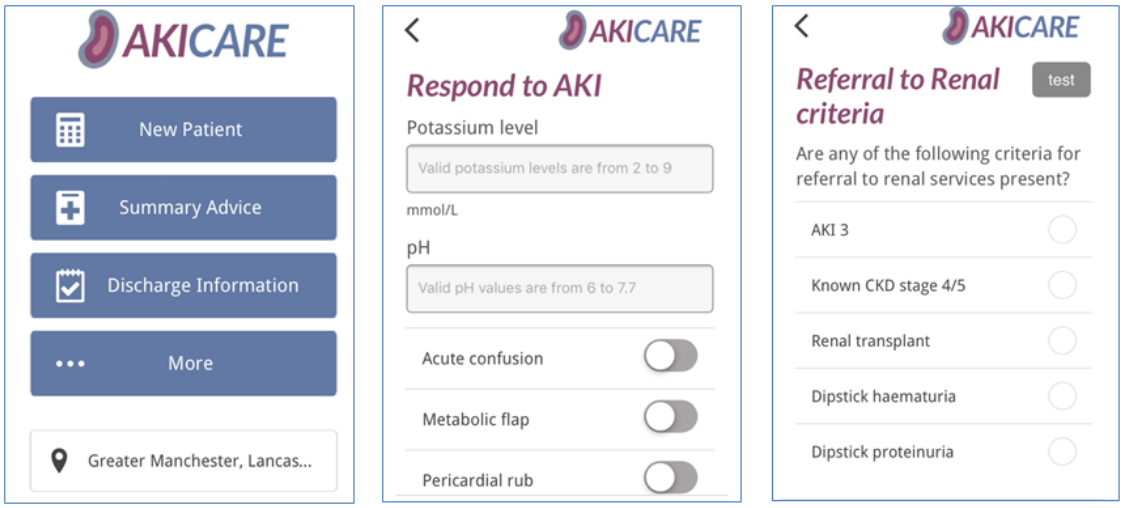
Development of the AKI care app included several groups including software developers, renal clinicians, doctors and pharmacists, and involvement of our local patient and public involvement (PPI) group. Iterations of the app were developed and assessed for their usability and accuracy with some important changes to mandatory forcing functions removed to allow more flexible use. The primary aim of development was to provide a free, user-friendly platform to help guide the identification and management of AKI locally in accordance with contemporaneous local guidelines.

7.4.2 Data analysis

Data entered into the app from launch to May 2017 were analysed. User demographic information (grade, specialty, geographical area of origin) is entered when individuals first open the app and are required to register their details. Other usage statistics (biochemical values entered, complications of AKI, click-through rates between screens, time spent on each part of the app, Figure 7-1) were recorded in order to understand the current reasons for use and to improve user experience.

These data were collected, with any null values or values likely to represent typographical error (e.g. pH <6.4 or >7.7) excluded. The number and nature of any adverse features were summarised.

Figure 7-1. Sample screenshot from the AKI care app



7.4.3 Ethical considerations

This was exempt from specific ethical approval as it was fully anonymised data, but anonymysation and data extraction occurred in accordance with local information governance policy.

7.5 Results

7.5.1 User profiles

157 people downloaded the app between May 2015 and May 2017. Where a user elected to enter their clinical background (n = 86), 24% of downloads were from junior doctors, 22% from consultants and 10% from nursing staff. 101 downloads (64.3%) were from the North West of England where the app was developed and publicized. Of the remaining downloads, geographical locations included other UK sites, Estonia, Colombia, and Italy.

The app was used 952 times between May 2015 and May 2017. 57 people (36.3%)

downloaded the app but had not used it during the evaluation period. 12 people (7.6%) used the app on more than 15 occasions.

7.5.2 AKI analysis

The distribution within each AKI stage for all of the 952 entry episodes was as follows: stage 0 (n = 268, 28.2%); stage 1 (n = 291, 30.5%); stage 2 (n = 118, 12.4%); stage 3 (n = 275, 28.9%). Within the app it is possible to "recognise AKI" through creatinine value, urine output, or by entering AKI stage, if known.

Creatinine was entered 1428 times, split between two different input boxes: baseline and peak creatinine. Mean baseline creatinine was 329 mcmol/L, mean peak creatinine was 312 mcmol/L, baseline creatinine ranged from 30 mcmol/L to 2000 mcmol/L and peak creatinine ranged from 30 mcmol/L to 1800 mcmol/L with a standard deviation of 314 mcmol/L for baseline creatinine and 261 mcmol/L for peak creatinine. Baseline creatinine is greater than peak creatinine due to the free text nature of the app which allows this data input error. For the entries of AKI 3 a baseline average creatinine was entered as 197.9 mcmol/L and a peak creatinine average of 212.6 mcmol/L.

Of the 550 (38.5%) creatinine entries the following were in increments of 100 (100 mcmol/L n = 32, 200 mcmol/L n = 37, 300 mcmol/L n = 38, 400 mcmol/L n = 14, 500 mcmol/L n = 235, 600 mcmol/L n = 16, 700 mcmol/L n = 115, 800 mcmol/L n = 34, 900 mcmol/L n = 6, 1000 mcmol/L n = 9, >1000 mcmol/L n= 14). These "round number" entries accounted for 75.5% of entries by frequent users (users with more than 15 entries as detailed above) and 82.1 % of occasional users (users with less than 15 entries). This is may represent the app being used for educational as well as clinical purposes, with these data probably indicating users exploring "what if" situations.

A previously known AKI stage was entered 201 times as follows: stage 0 (n = 28, 13.9%), stage 1 (n = 52, 25.9%), stage 2 (n = 42, 20.9%), and stage 3 (n = 79, 39.3%). The proportions between these distributions of AKI stages differ significantly from to our local data audited in 2015: stage 1 (n = 2316, 67%); stage 2 (n = 621, 18%); and stage 3 (n = 518, 15%).

7.5.3 Complications

A serum potassium value was entered on 372 occasions (63%). Normal serum potassium range is 3.5 -5.3 mmol/L with the renal association guidelines suggesting action be taken when the potassium is greater than 5.5 mmol/L.[9] The median potassium value recorded was 5.6 mmol/L. (range 2 - 9 mmol/L, IQR: 5 – 6.43 mmol/L). A pH value was entered 323 times (54%). When pH values of less than 6.4 or greater than 7.7 are excluded, the median pH value was 7.18 (range 6.4 – 7.7, IQR 7- 7.36).

The risk assessment tool within the app, which is generated following identification of an AKI, was completed 595 times. Of these, 393 (66%) were identified as having a physiological complication of AKI, These were: confusion - 148 (25%), uraemic flap - 85 (14%), pericardial rub - 66 (11%), pulmonary oedema - 92 (15%). Of those with complications, 25% had more than 1 complication, with 45 (11%) having all 4 complications.

7.6 Discussion

7.6.1 The AKI Care App

The AKI e-alert mandated by the National Patient Safety Alert in 2015 has superseded components of the AKI Care App particularly those related to identifying the AKI Stages. However, the app remains a useful educational and reference tool for symptoms recognition, safe transfer assessment, and signposting to appropriate services. This app preceded the AKI alert and now has relevance and utility as a decision support tool, allowing professionals to consider the patient holistically rather than in terms of a singular data point. This analysis highlights that medical apps for clinical use should be designed with this in mind and pre-emptively include an educational component.

The over-representation of AKI Stage 3 in comparison to both epidemiological studies[10] and our own internal audit data (39% vs 15%) is likely to represent either increased use for more severe stages of AKI or for educational inquiry. AKI is defined in this app through serum creatinine value. Urine output is an optional addition and rarely used by app users, which reflects clinical practice and published literature on AKI. Unfortunately despite our own quality improvement collaborative work within the trust, the fluid balance recording remains inconsistent, particularly

in uncatheterised patients outside of critical care environments.[11] One drawback in our trust is that the records remain manual paperwork rather than in-line with the rest of our online electronic patient records. There are always difficulties in measuring the urine output of patients who are incontinent or independently mobile as they frequently toilet themselves are not always able or empowered to engage with fluid balance monitoring.

As the AKI Care App was developed with a User Centred Design approach, there were several iterations prior to going live that prevented numerous faults. The app therefore has a simple interface and is user-friendly, with multidisciplinary appeal. Overall, it can deliver valuable information to users for identification, investigation of AKI and management of its complications. It also includes signposting to appropriate services for onward referral.

The nephrology community has previously developed apps to support management of hypertension, dialysis and transplantation, but nothing specific to AKI. The Royal College of Physicians of Edinburgh, in collaboration with NHS Kidney Care, have since developed an acute kidney injury app[12] to provide easy access to the national guidelines. However they have not collected demographic details, provided live decision support, nor published usage data. The London Acute Kidney Injury network has developed an app[13] with guidelines and non-interactive pathways for AKI with a contacts page for local renal services.

7.6.2 Wider implications for medical apps

There are generic rules and considerations that should be taken into account in the development and advocation of any medical app use.[14] Every Hospital Trust needs also to develop and maintain a "bring your own device" (BYOD) policy in terms of expectations for security and use of personal devices. Encryption and privacy must be explicit and monitored to maintain data security and comply with the data protection act. The development and ongoing iteration or modification of current apps should be considered in conjunction with the advice given by the NHS Open App library. We must consider the future of integrated apps versus standalone apps and the regulations for maintaining and updating these.

Worldwide there is a growing body of evidence from small studies to suggest that apps are acceptable to users and have the potential to effect change in behavior

amongst clinicians or patients.[15] The smartphone's portability and acceptability to the general public makes it a convenient and efficient tool for information interface at the point of care. However there is a need to consider the etiquette of mobile phone use, if used as a point of care testing tool. Does use of a smartphone during consultation impact on the doctor-patient relationship? And not only may the smartphone be a distraction in the workplace, it may also be a potential reservoir of pathogens.[16,17] The use of smartphone apps may stifle learning within the medical workplace, but smartphone use can encourage reflection and enhance the learning cycle.[18]

7.6.3 Future work

This app will continue to be promoted around the region and undergo updates as needed according to user feedback and guideline changes as needed. A secondary version of this app has been made specifically for colleagues working with a primary care setting or community setting with relevant material and signposting.

7.7 Limitations

There are limitations within the app itself due to non-compulsory elements for data input, therefore it is unknown if symptoms are truly negative or simply not inputted. This compromise for data gathering is a positive for user interaction as there are fewer compulsory elements to enter or interact with. Also in the original iteration of the app the range for input values was not set, therefore manual exclusion criteria were applied to ensure the same exclusion criteria were used throughout, as it is unclear whether pH values such as 2.0 or 8.0 were entered either in error or as an educational inquiry.

As yet there is no integration of the AKI care app with the IT systems in hospital that might allow self-population of any information. There is widespread concern among public bodies and pressure groups, and increasingly among the general public, about data and network security. Reliable security and accountability in the context of data sharing and distribution, automated or otherwise, is of paramount importance and subject to increasing scrutiny in the wake of the New Scientist coverage of the DeepMind collaboration with the Royal Free Hospital.[19] Here concerns were raised regarding the access and use of data of 1.6 million patients, and it was considered the

information was obtained on an "inappropriate legal basis" as it was used to test the AKI app "Streams" and not used in direct patient care.[20] Access to excess data for patients, many of whom did not have AKI, was granted without sincere and transparent dialogue with stakeholders, both clinicians and patients.

Transparency and an open dialogue in data collection and usage is imperative.[20,21] In addition the reliability of network coverage within most hospitals may be a challenge. The app may not show benefits over and above the now mandatory existing e-alert system, which highlights the risk of swift obsolescence in an ever-evolving world of technology.

7.8 Conclusion

Smartphones are acceptable to patient and physicians for personal use and have the potential to enhance care through supporting clinical decision-making, but are yet to attain widespread acceptability at the point of care. The AKI Care App can aid early recognition, investigation and management of patients with AKI. It has, however been superseded by the e-alert in our own laboratory system and therefore this simple, user-friendly app finds value as more of an educational than reference tool. This suggests we should not only plan for obsolescence but also to build in optional education or hypothetical entries to allow differentiation from "real world" entries. Medical apps are yet to establish themselves as either standalone tools or integrated NHS technology, and future successful app development relies on public, physician and executive support.

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Chapter 8

A comparison of point of care testing with gold standard laboratory testing in different clinical settings

8.1 Rationale

This chapter addresses the use of point of care (POC) testing for biochemical and haematological parameters, and the opportunities and challenges that it presents. It seeks to identify the reliability of POC testing compared to laboratory gold standards, and thereby consider their potential for wider use as well as their limitations. This work also prompts discussions on the medicolegal aspects of using POC tests to inform decision making or policy.

The work was initiated to aid in the management of hyperkalaemia, a known complication of acute kidney injury (AKI) previously discussed in the context of the AKI quality improvement collaborative (Chapter 6) and of the AKI Care App (Chapter 7). Hyperkalaemia has the potential to be immediately life threatening, and requires enhanced monitoring and management. This paper seeks to delineate those in whom it was safe to use POC testing to make immediate clinical decisions rather than have to wait for laboratory measurements. POC testing has the potential to aid faster decision-making and management. Measuring potassium and sodium values using POC testing may also allow clinicians to make more informed choices in respect of sodium and potassium content when prescribing intravenous fluid for resuscitation of patients with AKI. In a broader context, the use of POC testing also has the potential to improve the efficiency of patient flow and utilization of appropriate monitored beds.

8.2 Abstract

Introduction

Point of care (POC) tests can provide timely results that can positively influence care upon presentation or in the acutely unwell patient. There have been studies showing reliable correlation between POC tests and gold standard laboratory measurements. However there are no guidelines supporting their use in clinical practice. This chapter looks at the reliability and clinical applications of POC tests in a real-world setting.

Methods

We analysed paired blood samples taken within one hour of admission to the emergency department for POC testing and laboratory values. Anonymised data was extracted from the 'data warehouse' for age, gender, admission diagnosis, AKI stage or renal status, along with paired values of potassium, sodium and haemoglobin. This data was then analysed for bias, precision and clinically relevant factors, such as the percentage of patients with hyperkalaemia on a POC who also had hyperkalaemia on a laboratory sample.

Results

The POC tests were best correlated in the normal range. Only 2.6% of normal POC potassium results were high on laboratory samples, which could lead to meaningful changes in management plans. Sodium samples were well correlated over a range of 125-145mmol/l but not sensitive enough in lower ranges for monitoring or safe hyponatraemia correction. POC testing for haemoglobin showed that only 2.5% of laboratory values were low if the POC test was normal, which is reassuring for delaying transfusion or supporting safe discharge.

Conclusion

Overall our analyses suggest scenarios in which POC testing can safely be used, with clinical correlation, to influence more timely patient management and improve the efficiency of patient flow and effective and appropriate use of monitored beds.

8.3 Introduction

Point of care (POC) tests in the form of arterial or venous blood gas sampling are a key investigation to assess or monitor acutely unwell patients. They provide a breadth of information that is not available on other standard laboratory testing (such as pH, partial pressures of carbon dioxide and oxygen) and have the advantage of providing very rapid results.

They also provide overlapping results with laboratory samples, such as electrolytes and haemoglobin. Reliable correlation of these between POC and laboratory tests would allow clinicians to deliver and alter management more swiftly, potentially improving outcomes for patients and improving patient flow.[1] In a survey conducted in hospitals in the USA, 92% of clinicians felt turnaround was improved by POC testing. However 73% had concerns of about accuracy, and were thus reluctant to place sole reliance on POC results.[2] There has been work looking at low levels of confidence in the reliability and accuracy of POC testing which showed that 38% of clinicians did not trust POC tests and only 44% would take responsibility for them.[3] This resonates with the work done by the Oxford Diagnostic Horizon scan programme, which found that only 18% of the 500 studies it analysed have evaluated the clinical effectiveness of POC testing, with a median time from introduction to evaluation of over 9 years.[4] Therefore, at present clinicians do not generally consider it safe to be guided by the initial POC test result, but prefer to wait for the laboratory result to initiate management.

Several small studies have showed mixed results when considering the POC tests for potassium, sodium and haemoglobin. An Australian study of 352 patients saw over 90% of potassium values and over 95% of sodium and hemoglobin values lay within clinically acceptable limits (potassium +/-0.5mmol/l, sodium +/-5mmol/L and haemoglobin +/-10g/dL), with a bias of 0.21mmol/L for potassium, 0.6mmol/L for sodium and 16g/L for haemoglobin.[5] However, an Indian ED-based study of 112 patients, a Turkish ICU-based study of 84 patients and a Greek ICU-based study of 31 patients all found both sodium and potassium correlation to be outside of acceptable limits.[6–8] Two further Turkish studies of 100 patients and of 40 patients respectively and an Indian study of 200 patients all concluded that sodium correlations were unacceptable but that potassium was better correlated and suitable for clinical use. [9–11]

Conversely, a Chinese Emergency Department (ED) study of 200 patients found that potassium, sodium and haemoglobin all fell within acceptable limits (according to USCLIA-limits [12]).[13] A London study of fewer than 200 patients also felt that potassium, sodium and haemoglobin were suitable for POC interpretation when taken in clinical context.[14]

Perhaps the most frequent use of POC gas sampling is at the point of patient arrival in an ED. Here, patients frequently have both an arterial or venous blood gas and venous blood samples drawn simultaneously. In the majority of NHS hospitals in England, the blood gas sample is processed in the ED, whilst the venous samples are sent to the laboratory autoanalysers via a pneumatic air pod system or via portering. The blood gas analysers analyse whole blood that has been taken and homogenised in a heparin syringe, whereas the autoanalysers process the serum from vacutainer bottles with fixed diluents. POC results provided in this setting may inform clinicians of abnormalities that require immediate attention and where the acuity of illness means that waiting more than one hour for a laboratory sample results is potentially dangerous.

Other clinical scenarios arise where urgent delivery of a result is of less clinical importance, but where the standardized use of POC testing may allow for more immediate results than laboratory testing, with the positive outcome of improved patient flow or reduced bed occupancy. Examples are re-assessment of potassium or sodium values after treatment for hyperkalaemia in acute kidney injury, or for hyponatraemia in cases where repeat dosing, determination of the need for cardiac telemetry, or even discharge are being considered. Results may also allow clinicians to make more informed decisions about intravenous fluid preparation choices during resuscitation for conditions such as AKI — assuming up-to-date electrolytes are available from POC measurements.

The aim of this study was to evaluate the potential safety of treating or devising management plans or policy based on rapidly available POC tests in comparison to awaiting the gold standard laboratory results. Tests chosen for this study were potassium, sodium, and haemoglobin. These were chosen as they represent three of the most common tests where the immediacy of results have significant implications in terms of both clinical treatment and patient flow.

Potassium is the principle intracellular cation and is important for maintaining membrane electrical potential particularly in neuromuscular tissues. It also contributes to the acid-base balance. Potassium derangements can lead to muscle weakness and cardiac arrhythmias, the latter often necessitating cardiac telemetry below or above certain threshold values. Sodium is the major extracellular cation that determines extracellular fluid osmolality and volume. It is controlled through dietary intake and renal excretion. Derangements can lead to confusion, seizures or coma. Haemoglobin is the oxygen-carrying protein found in red blood cells. Acute changes in haemoglobin can suggest significant haemorrhage.

This study looks at a large real-world dataset performance of the correlation between the POC and autoanalyser results in a single Acute Hospital Trust in the UK. Overall, this may facilitate swifter management for acutely unwell patients or safe, earlier discharges from ED in certain patient populations.

8.4 Methods

8.4.1 Samples

Samples were taken from acute patient admissions to the Salford Royal Foundation Trust ED. In this Trust, all patient in the majors area of ED have simultaneous venous gas sampling and standard laboratory sampling taken from the same site on arrival. The method of collection is either direct vessel puncture with a needle and vacutainer, or heparinized syringe attached via cannula. Samples are taken by a range of multidisciplinary staff including appropriately trained healthcare assistants, nursing staff, advanced nurse practitioners and doctors of all grades. The samples are then homogenized by gently agitating. The serum samples are sent via pod to the laboratory. The blood gas samples are analysed immediately in the department.

8.4.2 Analysers

The POC tests are completed on Roche B221 analysers. We have only included samples taken after 15 December 2016, as the Hospital changed blood gas analysers at this time, switching from the Radiometer ABL 800 series analysers to the Roche B221 analysers. These analysers have three calibration modes: a system calibration every 24 hours, a one-point calibration hourly, and a two-point calibration every 12

hours. The quality control results are acceptable if they come within two standard deviation of the ranges on the analyser.

The serum blood samples are analysed on the automatic analysers in the laboratory. Since January 26 2015 the hospital has been using Siemens Advia analysers that use an assay based on ion selective electrodes.

8.4.3 Data extraction

The blood test results were extracted from the Trust 'data warehouse' using Structured Query Language (SQL). The extraction process captured all acute admissions that occurred via attendance at the ED over 32 months from 01/01/2016 to 29/08/2018. All data extracted, including this and other measured parameters, was anonymised on extraction .

The first point of care test in ED was identified for potassium, sodium, and haemoglobin. Each POC test was then linked to the nearest serum sample sent to the laboratory. Paired results included only those where the two samples were collected less than 60 minutes apart, on the presumption that this represented results from the samples taken together.

Alongside these laboratory and POC data, other parameters recorded were: whether patients were registered as a dialysis patient or previous transplant; if there was a renal episode (coded review by senior nephrologist) during the admitted spell or if the patient has had a renal outpatient attendance with the 12 months prior to arrival; the concurrent presence of an acute kidney injury (AKI); the admission reason; and the age and gender of the patient.

8.4.4 Data analysis

Comparisons were made between all of the paired results for the POC analysers and gold standard laboratory tests for potassium, sodium and haemoglobin, within the time frames outlined above. Firstly, a Bland Altman approach was taken. Here, a negative bias represents a higher test result by the laboratory compared to results from POC testing. Comparisons were made between paired samples in all patients and then in sub-groups separated according to the following factors: renal function (no AKI, AKI stage 1, AKI stage 2, AKI stage 3 or known dialysis patients); ICD 10 coded admission diagnoses of sepsis, stroke (CVA), chronic obstructive pulmonary

disease (COPD), gastrointestinal bleed (GIB), urinary tract infection (UTI); age group (<18. 18-54, 55-64, 65-74, 75-84, >85); and gender.

Next, we calculated the likelihood of POC and laboratory tests providing comparable results in terms of being normal, high or low according to reference ranges or treatment thresholds. For this, we calculated four clinically relevant outcomes:

- If the POC sample value was low, was the laboratory sample value normal?
- If the POC sample value was normal, was the laboratory sample value low?
- If the POC sample value was normal, was the laboratory sample value high?
- If the POC sample value was high, was the laboratory sample value normal?

The definitions of low, normal and high values used for each test were as follows:

- Potassium (<3.5mmol/L, 3.5-5.3 mmol/L, >5.3 mmol/L respectively)
- Sodium (<135mmol/L, 135-145mmol/L, >145mmol/L respectively)
- Haemoglobin (<110g/L, 110-150 g/L, >150 g/L respectively)

As per the Bland Altman analyses, this was performed across the whole population and then in the sub-groups described above. The IBM Statistical Package for the Social Sciences (SPSS) version 23 for Mac [SPSS (UK) Ltd, Woking, Surrey, UK] was used for all analyses.

8.5 Ethical considerations

This study was exempt from specific ethical approval as it is part of a quality improvement project and the data was fully anonymised in accordance with data protection guidelines.

8.6 Results

8.6.1 Potassium

There were 9630 paired POC and laboratory samples for potassium values as shown in Table 8-1. The bias was positive and indicates that the laboratory values read lower than the POC samples. The overall bias (mean difference between laboratory and POC results) was 0.28 mmol/L, with a precision (standard deviation of this difference) of 0.39 mmol/L. For specific sub-groups of patients, the bias differed in

the range of 0.23-0.31mmol/L. There were 869 AKI episodes within these paired values. Within these groups, and in comparison to dialysis patients, the bias was broadly similar. There was a high degree of precision in dialysis patient samples (0.21 mmol/L), but very poor precision in patients with AKI 1 (0.57 mmol/L).

In a comparison of bias and precision between different presenting diagnoses, ages, and genders, the bias and precision values were broadly comparable between all sub-groups (Table 8-1).

Table 8-1. Potassium values comparing laboratory to POC testing

	Bias (mean diff)	Precision (SD of mean diff)	Count
Overall	0.28	0.39	9630
AKI			
AKI 0	0.28	0.38	8761
AKI 1	0.26	0.57	533
AKI 2	0.31	0.31	197
AKI 3	0.23	0.29	139
Dialysis	0.27	0.21	112
Diagnoses			
Sepsis	0.25	0.36	855
CVA	0.29	0.32	234
COPD	0.31	0.28	857
GIB	0.30	0.26	174
UTI	0.28	0.32	227
Age groups			
<18	0.25	0.45	276
18-54	0.28	0.42	3220
55-64	0.29	0.37	1231
65-74	0.28	0.46	1639
75-84	0.30	0.28	1902
>85	0.28	0.34	1362
Gender			
Male	0.26	0.40	4962
Female	0.31	0.37	4668

Key: SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection, results for potassium shown in mmol/L

Table 8-2 shows that if a POC potassium test is normal then the laboratory results are almost always normal as well. If the POC test is normal, only 0.4% of laboratory values are low and only 2.6% are high: there is a high agreement with the laboratory value. However, in the 62.5% of cases where POC potassium results were low, the laboratory values were normal. Similarly, in the 26.6% of cases of a high POC values, laboratory results were normal.

If the POC potassium is low, as AKI stage increases, it is more likely to be reliable (AKI 0 = 61.6% normal laboratory value, AKI 3 = 29.4%). Likewise, if the POC test potassium is high there is an increasing chance that this is true in comparison to the laboratory potassium value (AKI 0 = 34% to AKI3 2.4% and dialysis 0%). There is an increasing chance of the laboratory value reading high with increasing AKI stage, even if the POC test is normal (AKI 0 1.9% to AKI 3 12.3%). Clinically of note, for patients with AKI 3 and normal POC results, 12.3% will actually have high laboratory potassium values.

There were insufficient patients with a high POC result and a normal laboratory value (less than 10) in each of the diagnosis groups to perform reliable comparisons (labelled as not applicable or N/A in the table). This is due to timing of lab samples and POC groupings as these are common diagnoses where the majority of patients are stable and would not warrant POC testing at the front door.

Age also affected the extremes of results, with younger patients very unlikely (70.4%) to have a true low potassium reading on POC testing in comparison to over 85s (57.7%). Younger patients were less like to have a true high reading in their POC testing (42.9%) in comparison to older age groups. Those aged 75-84 yielded only 15.6% of high POC tests with normal laboratory values.

There was no significant difference between genders.

Table 8-2. The percentage of POC tests which were accurate when compared to laboratory testing in different ranges of potassium (low, normal, high)

	POC result low, laboratory value normal	POC result normal, laboratory value low	POC result normal, laboratory value high	POC result high, laboratory value normal
Overall	62.5%	0.4%	2.6%	26.6%
AKI				
AKI 0	61.6%	0.4%	1.9%	34.0%
AKI 1	58.1%	0.0%	8.9%	17.0%
AKI 2	52.4%	0.8%	7.7%	8.0%
AKI 3	29.4%	1.2%	12.3%	2.4%
Dialysis	45.5%	0.0%	5.6%	0.0%
Diagnoses				
Sepsis	56.1%	0.3%	3.5%	67.9%
CVA	76.7%	0.0%	3.0%	N/A
COPD	60.3%	0.3%	1.3%	N/A
GIB	57.6%	0.0%	2.2%	N/A
UTI	61.4%	0.0%	5.1%	N/A
Age groups				
<18	70.4%	0.0%	8.5%	42.9%
18-54	65.9%	0.6%	0.7%	36.8%
55-64	58.4%	0.2%	2.6%	20.0%
65-74	62.4%	0.3%	2.6%	27.7%
75-84	61.0%	0.3%	3.8%	15.6%
>85	57.7%	0.5%	3.8%	29.3%
Gender				
Male	62.4%	0.4%	2.7%	24.4%
Female	62.5%	0.3%	2.4%	30.1%

Key: POC = point of care, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection, N/A indicates fewer than 10 patients in this group

Table 8-3 shows that the mean laboratory potassium was 4.24mmol/L with a mean POC value of 3.94mmol/L (normal range 3.5-5.3mmol/L). These data show an increase in the both the mean potassium value and the standard deviation for potassium values as the AKI stages increase. The mean potassium value increases from 4.20 to 5.01mmol/L, and from 3.9 to 4.78mmol/L for laboratory and POC measurements respectively, from no AKI to AKI stage 3. In the laboratory measurements the standard deviation increases from 0.58mmol/L in AKI stage 0, to 1.20mmol/L in AKI stage 3.

Patients aged under 18 years showed the highest mean levels of potassium both in laboratory and POC testing (4.44mmol/L, 4.19mmol/L), yet elsewhere potassium values increased with age (from 4.11 to 4.33mmol/L moving from the 18-54 years group to the >85 years group for laboratory values, and 3.81 to 4.04mmol/L for the respective POC values). As the potassium value increased with age, there was an increase in the standard deviation for both laboratory and POC values (0.35 to 1.01mmol/L, 0.32 to 0.69mmol/L).

Women had slightly lower levels of potassium on both laboratory and POC testing in comparison to men (4.17 versus 4.30mmol/L, 3.85 versus 4.02mmol/L).

The Bland-Altman plot in Figure 8-1 shows the correlation between potassium laboratory values and point of care testing. It demonstrates that the laboratory readings are generally higher and that the majority of results are within the normal range. The low potassium readings are rarely higher on the laboratory samples, however the higher values show much more spread which could be of clinical significance.

Figure 8-1. Bland-Altman plot of laboratory and point of care testing potassium values

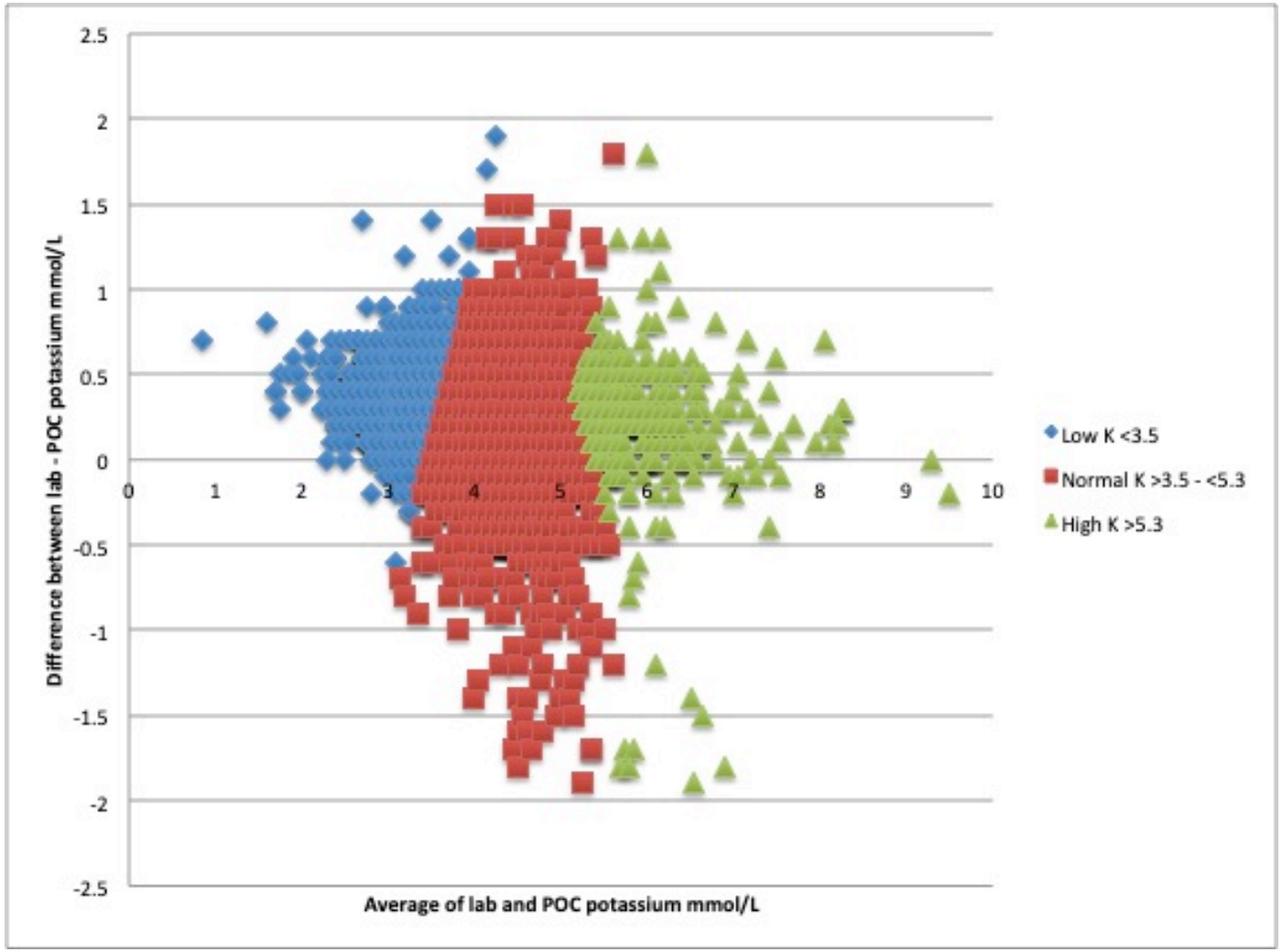

Table 8-3. Comparison of mean and standard deviations of laboratory and POC potassium values

	Mean K lab	SD K lab	Mean K POC	SD K POC	Mean of Kdiff	SD of Kdiff	Count of K
Overall	4.24	0.63	3.94	0.67	0.30	0.26	9583
AKI							
AKI 0	4.20	0.58	3.90	0.62	0.30	0.26	8719
AKI 1	4.47	0.81	4.18	0.86	0.29	0.30	529
AKI 2	4.50	0.93	4.18	0.96	0.32	0.26	196
AKI 3	5.01	1.20	4.78	1.25	0.23	0.29	139
Dialysis	5.08	1.30	4.82	1.33	0.27	0.21	112
Age							
<18	4.44	0.65	4.19	0.63	0.26	0.35	274
18-54	4.11	0.55	3.81	0.58	0.30	0.26	3199
55-64	4.23	0.69	3.93	0.73	0.30	0.25	1227
65-74	4.26	0.64	3.96	0.68	0.30	0.26	1627
75-84	4.34	0.65	4.04	0.69	0.30	0.26	1898
>85	4.33	0.64	4.04	0.69	0.29	0.28	1358
Gender							
Male	4.30	0.64	4.02	0.67	0.28	0.27	4935
Female	4.17	0.62	3.85	0.65	0.32	0.26	4648
Ranges (mmol/L)							
K <3.5	3.50	0.35	3.11	0.32	0.39	0.20	1849
K 3.5-4.9	4.31	0.38	4.01	0.36	0.30	0.23	7119
K 5-6.5	5.45	0.57	5.40	0.37	0.06	0.49	560
K>6.5	7.02	1.01	7.17	0.69	-0.15	0.70	55

Table 8-3 Key: SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection, results for potassium shown in mmol/L

8.6.2 Sodium

Overall there were 11574 paired POC and laboratory sodium samples, shown in Table 8-4. Within the whole population the bias was -1.07mmol/L, and the precision 1.90mmol/L. In the context of a whole population mean laboratory sodium value of 137mmol/L, this represents very strong concordance between POC and laboratory values. The negative bias indicates that overall the POC results give a slightly lower value for sodium in comparison with the laboratory reading.

The lowest bias sub-group was patients undergoing haemodialysis. Here, the bias was just -0.02mmol/L. These patients also showed a higher degree of precision in comparison to non-dialysis patients with or without AKI (1080 and 10494 events respectively). The sub-groups with the poorest bias were the age group 18-54 years and patients with stroke. Alongside this, with increasing age there was decreasing bias observed in adults within the data, -1.57mmol/L in those between 18 and 54 years, to -0.66mmol/L in those over 85 years of age. There were similar degrees of bias and precision between genders. For different diagnoses, the sodium values in patients admitted with sepsis (-0.68mmol/L) and COPD (-0.34mmol/L) showed significantly less bias than those admitted with stroke (-1.57mmol/L).

Overall sodium laboratory values and POC values showed a high level of clinical correlation (Table 8-5). There were very few events where the POC test read high and the laboratory value was normal, and there was only a 0.2% chance of the POC test being normal and the laboratory test being high. Lower POC values were less accurate but had less than a 10% error overall.

Paired samples in AKI 3 where the POC test showed low sodium were rarely incorrect (4.3%) in comparison to those in patients on dialysis (17.5%). Conversely patients with neither AKI nor normal POC results were less likely (9%) to have a low laboratory value than those with an AKI 3 (19.8%).

Patients with a UTI were less likely (6.7%) to have a low POC sodium and a normal laboratory value than patients with COPD (14.4%). The numbers of patients with high POC tests in the different diagnoses were lower than 10 and were excluded from analysis, marked not applicable (N/A). Qualitatively, neither gender nor age had significant influence on the results.

Table 8-4. Sodium values comparing laboratory to POC testing

	Bias	**Precision**	**Count**
Overall	-1.07	1.90	11574
AKI			
AKI 0	-1.11	1.87	10494
AKI 1	-0.81	2.17	655
AKI 2	-0.46	1.95	246
AKI 3	-0.72	2.24	179
Dialysis	0.02	1.58	144
Diagnoses			
Sepsis	-0.68	1.77	1041
CVA	-1.57	1.72	92
COPD	-0.34	2.11	470
GIB	-1.10	1.87	202
UTI	-1.06	1.68	267
Age groups			
<18	-1.31	1.73	307
18-54	-1.57	1.91	3782
55-64	-1.14	2.01	1492
65-74	-0.78	1.83	1976
75-84	-0.73	1.81	2332
>85	-0.66	1.72	1685
Gender			
Male	-1.12	1.88	5878
Female	-1.02	1.91	5696

Key: SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection

Table 8-5. The percentage of POC tests which were accurate when compared to laboratory testing in different ranges of sodium (low, normal, high)

	Likelihood of a low laboratory value when POC result is normal	Likelihood of a high laboratory value when POC result is normal	Likelihood of a normal laboratory value when POC result is low	Likelihood of a normal laboratory value when POC result is high
Overall	8.9%	0.2%	9.7%	0.0%
AKI				
AKI 0	9.0%	0.2%	9.8%	0.0%
AKI 1	13.6%	0.7%	9.2%	0.0%
AKI 2	14.6%	1.5%	8.6%	0.0%
AKI 3	19.8%	0.0%	4.3%	0.0%
Dialysis	14.9%	N/A	N/A	N/A
Diagnoses				
Sepsis	13.8%	0.5%	10.5%	N/A
CVA	5.8%	0.0%	12.1%	N/A
COPD	7.1%	0.6%	14.4%	N/A
GIB	6.2%	0.0%	8.7%	N/A
UTI	10.8%	0.0%	6.7%	N/A
Age groups				
<18	6.7%	N/A	N/A	N/A
18-54	7.6%	0.2%	9.5%	0.0%
55-64	10.5%	0.1%	7.9%	0.0%
65-74	10.1%	0.3%	9.9%	0.0%
75-84	9.8%	0.2%	9.6%	0.0%
>85	8.7%	0.4%	10.5%	0.0%
Gender				
Male	9.1%	0.3%	8.5%	0.0%
Female	8.7%	0.2%	10.9%	0.0%

Key: SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection, N/A indicates fewer than 10 patients in this group

Over the 11556 paired samples, sodium was found at the lower end of the normal range (135-145mmol/L), with 136.9mmol/L as seen in Table 8-6.

There was an increasing standard deviation of the sodium values seen as AKI stage increased from AKI 1 to AKI 3, particularly in the laboratory sample values (4.6 to 9.5mmol/L). Age and gender showed close correlation between both laboratory and POC testing. Slightly low (125-134mmol/L) and normal (135-145mmol/L) sodium values were better correlated with smaller standard deviations that those at the more extreme ranges.

The Bland-Altman plit in Figure 8-2 demonstrates the correlation between laboratory and point of care testing for sodium values. There is variability of up to 8mmol/L which is within tolerable limits for clinical use however not for sodium correction which requires much more accurate results.

Figure 8-2. Bland-Altman plot of laboratory and point of care testing sodium values

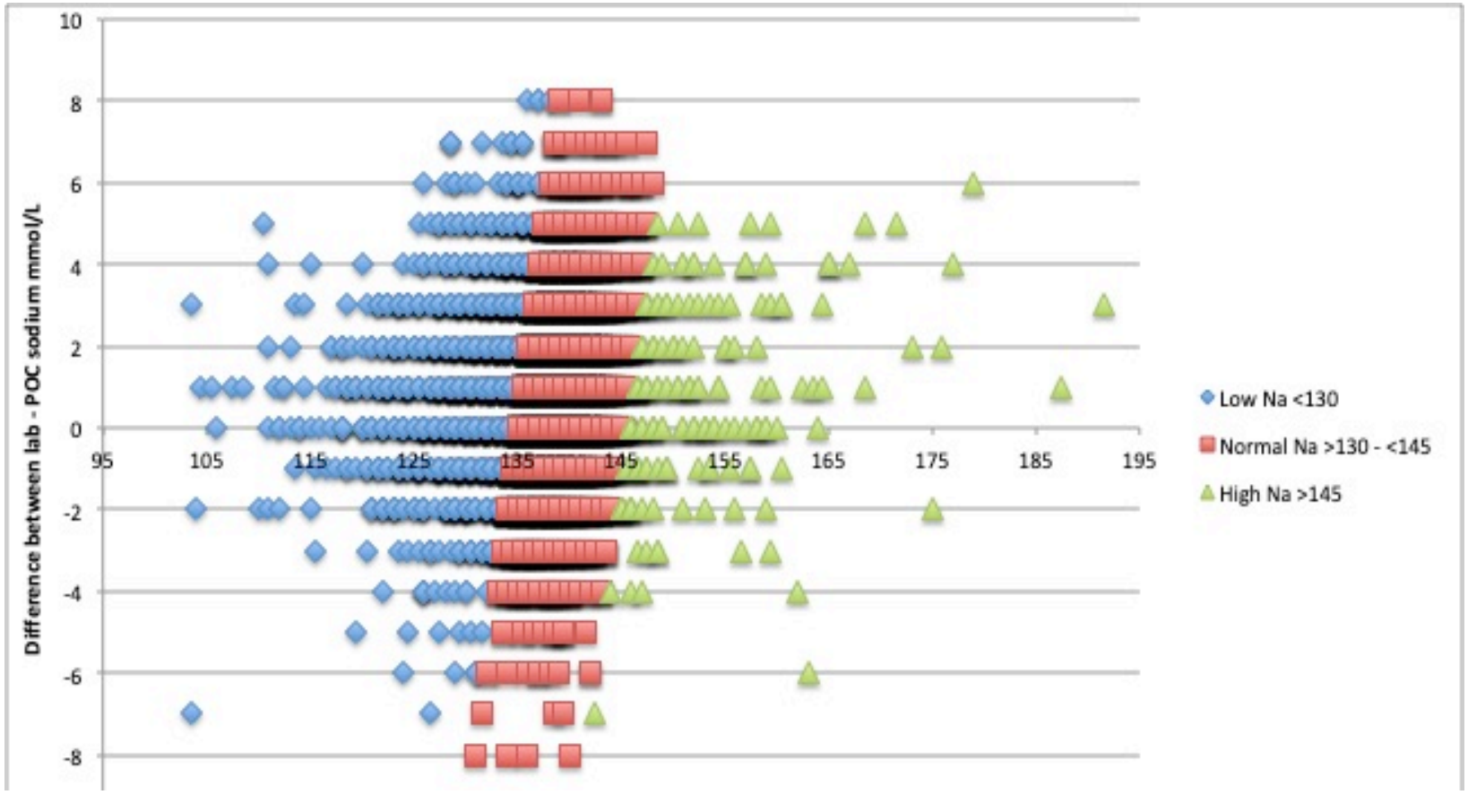

Table 8-6. Comparison of mean and standard deviations of laboratory and POC sodium values (lab = laboratory, SD = standard deviation, diff = difference, Na = sodium, AKI = acute kidney injury)

	Mean Na lab (mmol/L)	SD Na lab (mmol/L)	Mean Na POC (mmol/L)	SD Na POC (mmol/L)	Mean of Na diff (mmol/L)	SD of Na diff (mmol/L)	Count of Na diff
Overall	136.9	5.0	137.9	5.2	1.07	1.85	11556
AKI							
AKI 0	137.0	4.6	138.1	4.9	1.11	1.83	10482
AKI 1	135.9	6.1	136.7	6.1	0.83	1.91	651
AKI 2	136.3	9.5	136.7	9.5	0.46	1.95	246
AKI 3	136.2	9.5	136.8	9.7	0.62	2.02	177
HD	134.6	3.9	134.6	4.1	-0.02	1.58	144
Age							
<18	137.8	2.8	139.1	3.1	1.31	1.73	307
18-54	137.4	4.2	139.0	4.6	1.56	1.88	3776
55-64	136.0	5.5	137.1	5.7	1.12	1.86	1486
65-74	136.2	5.0	137.0	5.2	0.78	1.79	1974
75-84	136.7	5.2	137.4	5.4	0.74	1.77	2330
>85	137.2	5.8	137.9	5.9	0.66	1.68	1683
Gender							
Male	136.9	5.1	138.0	5.3	1.11	1.85	5868
Female	136.9	4.9	137.9	5.2	1.03	1.85	5688
Na ranges (mmol/L)							
Na<125	119.9	5.0	119.9	4.7	0.02	1.96	195
Na125-134	131.1	3.0	131.4	2.4	0.33	1.85	2088
Na 135- 145	138.1	2.6	139.4	2.6	1.20	1.75	8906
Na >145	147.6	7.3	150.2	6.7	2.59	2.27	367

Table 8-6 Key: Na = sodium, POC = point of care, diff – difference, SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, Na ranges in mmol/L

8.6.3 Haemoglobin

Table 8-7 shows that overall there were 5375 paired haemoglobin samples. The overall bias was negative (-1.11g/L), indicating that the POC test values are generally lower than laboratory values. The bias for individual sub-groups ranged from -0.40g/L to -4.63g/L. Precision also varied greatly from 4.27g/L to 12.10g/L. AKI 3 and dialysis patients showed very poor precision compared to other groups, including less marked AKI. The values for these were 12.10 and 12.03g/L respectively. By comparison, the precision for patients with no AKI was 6.15g/L. Patients with a gastrointestinal bleed showed less bias (-0.40g/L) but worse precision (9.49g/L) compared to other presenting diagnoses. For example, the values for COPD were bias -2.56, and precision 4.27g/L. Bias was much greater in the younger age groups (<18years = -4.63g/L, 18-54 years = -1.51g/L) than the older age groups (>85 years = -0.36g/L). There were no differences between patients of different gender.

Table 8-8 shows that overall the POC test performed best in the normal range where only 3.2% of normal POC results were actually low on laboratory testing, and only 1.4% of results were high in the corresponding laboratory samples.

Patients with either no AKI or AKI stage 1 or 2 had a greater chance of the POC haemoglobin reading low (11.5%, 14.1% and 16.7% respectively) compared to the laboratory value in comparison to patients with AKI 3 and dialysis patients (3.4% and 5.3%). However, patients without AKI were less likely to have normal POC haemoglobin and a low laboratory value (2.8%) than any other AKI or haemodialysis patient.

Patients diagnosed with a UTI were the most likely patient group to have a normal haemoglobin if their POC haemoglobin was recorded as being low (20%). For example, the respective values for sepsis and stroke were 11.7% and 0%. Patients

with a UTI were also more likely than any other diagnosis to have low laboratory haemoglobin if their POC was normal (9.8%).

Of potential clinical importance, patients with gastrointestinal bleeds were the least likely to have a low laboratory test result after normal POC haemoglobin (2.5%), which suggests a normal POC result for haemoglobin is reassuring in this setting.

Patients under 18 years had a greater risk of low haemoglobin on the laboratory sample, even in the setting of a normal POC value (9.7%), in comparison to all other age groups (range 1.5-4.9% for older patient groups). Patients over 85 years were more likely to have normal laboratory haemoglobin if their POC was high (30.8%) than their younger counterparts (18-54 and 55-64 years both 13.5%). There was no difference between genders.

Table 8-7. Haemoglobin values comparing gold standard laboratory to point of care testing.

	Bias	**Precision**	**Count**
Overall	-1.11	6.41	5375
AKI			
AKI 0	-0.95	6.15	4187
AKI 1	-1.24	8.71	310
AKI 2	-1.09	7.98	107
AKI 3	-0.87	12.10	92
Dialysis	0.61	12.03	66
Diagnoses			
Sepsis	-0.41	7.12	392
CVA	-2.56	4.82	104
COPD	-0.97	4.27	202
GIB	-0.40	9.49	88
UTI	-1.69	5.73	122
Age groups			
<18	-4.63	5.56	165
18-54	-1.51	5.92	1742
55-64	-0.68	7.74	687
65-74	-0.85	6.36	962
75-84	-0.95	5.98	1068
>85	-0.36	6.69	751
Gender			
Male	-1.45	6.34	2773
Female	-0.74	6.46	2602

Key: SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection.

Table 8-8. The percentage of POC tests which were accurate when compared to laboratory testing in different ranges of haemoglobin (low, normal, high)

	POC result low, laboratory value normal	POC result normal, laboratory value low	POC result normal, laboratory value high	POC result high, laboratory value normal
Overall	11.7%	3.2%	1.4%	17.1%
AKI				
AKI 0	11.5%	2.8%	1.5%	17.2%
AKI 1	14.1%	5.8%	1.7%	20.9%
AKI 2	16.7%	8.1%	0.0%	33.3%
AKI 3	3.4%	4.4%	2.2%	22.2%
Dialysis	5.3%	8.3%	4.2%	N/A
Diagnoses				
Sepsis	11.7%	4.6%	1.0%	24.2%
CVA	0.0%	7.7%	2.6%	9.7%
COPD	18.8%	5.9%	0.0%	14.1%
GIB	13.3%	2.5%	0.0%	16.7%
UTI	20.0%	9.8%	0.0%	40.0%
Age groups				
<18	9.1%	9.7%	0.0%	20.0%
18-54	14.0%	1.5%	1.3%	13.5%
55-64	12.5%	3.8%	2.2%	13.5%
65-74	9.5%	2.0%	1.8%	18.1%
75-84	10.0%	4.9%	1.7%	25.3%
>85	12.9%	3.3%	0.4%	30.8%
Gender				
Male	10.5%	3.6%	1.8%	14.4%
Female	12.8%	2.9%	1.1%	24.0%

Key: POC = point of care, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, CVA = cerebrovascular accident, COPD = chronic obstructive pulmonary disease, GIB = gastrointestinal bleed, UTI = urinary tract infection, N/A indicates fewer than 10 patients in this group

Table 8-9 quantifies the comparable mean haemoglobin values between POC and laboratory results (129.3g/L laboratory, 130.6g/L POC). The standard deviations were also similar (21.9g/L, 23.2g/L).

Mean haemoglobin levels dropped significantly with worsening renal function, from AKI 0 to AKI 3 and in haemodialysis patients (129.9 g/L, 119.5 g/L, 108.3 g/L) and also declined with age in adults (135.5 g/L to 121.8 g/L).

The standard deviation for patients with haemoglobin in the different ranges varied from 9.0g/L to 12.6 g/L in the laboratory results and from 8.0 g/L to 12.8 g/L in the POC testing. There was an expected difference in gender: male 132.7 g/L, female 125.7 g/L. Standard deviation was consistent between laboratory and POC testing throughout.

The Bland- Altman plot in Figure 8-3 demonstrates the differences between the laboratrory and haemoglobin point of care testing values. These are within 20g/dL and therefore show point of care testing to be accurate enough for clinical use, however in lower extremes would encourage laboratory correlation to advise for non-urgent blood transfusions.

6.7.5 Badges, stickers, information boxes

Different wards decided to create different ways of highlighting or managing patients with AKI. They developed magnetic badges for the patient allocation board, the boards behind each patient bed. They also created brightly coloured filing boxes to keep together AKI-related items such as printed information like the bundle assessments, fluid balance sheets and the patient information leaflets. These were of variable success because of staff rotation, so routine use of this strategy was abandoned.

6.7.6 AKI nurse champions

PDSA 1: Volunteer/nominated nurse champions attended learning sessions on behalf of their wards. They underwent additional training from the QI team and the learning and development team to gain more knowledge about AKI, QI theory and support in relaying this back to their base ward.

This QI project has taken place during a period of unprecedented demand on the NHS and staffing. Recruitment and retainment are issues affecting all areas of the Trust, and, as a result it has been especially difficult to get both regular and reliable attendance by named individuals at these organised learning sessions. Despite email reminders to both individuals and ward managers and physical walk rounds to ensure attendance, it has been increasingly difficult to maintain a turnout.

PDSA 2: The learning sessions were reduced from full day to half day or shorter sessions.

6.7.7 Junior doctor AKI champions

PDSA 1: A select group of self-declared interested foundation doctors.

Owing to four-monthly job rotations this was significantly less effective as an intervention than anticipated. The improvement work was also not fully supported from all wards, with poor buy-in from some senior clinicians. This created a significant barrier to supporting doctors or nurses working as AKI champions within these environments.

6.7.8 Electronic patient record (EPR) AKI documentation

Several changes to the EPR were made.

PDSA 1: AKI assessment and AKI pharmacy assessment documents.

PDSA 2: An automated insertion on to the post-take ward round for AKI assessment.

PDSA 3: Discharge documents automatically alerted the need for AKI coding.

PDSA 4: An algorithm is being developed for automated advice on phlebotomy timing after discharge, based on stage and resolution of AKI.

An audit of completion of the AKI bundle document shows that use of the AKI document within 24 hours of first AKI e-alert by medical staff is at 1.9% (380 assessments completed for 19,699 AKI episodes). This clearly indicates that the AKI document itself is not responsible for the improvements seen.

6.8 Results

Over the course of the Collaborative work there was a trend towards an increase in total episodes of AKI, in particular AKI stage 1 (Figure 6-4). These data remained within the limits of normal variation, with an average incidence of 277 AKI episodes per month.

Table 8-9 Key: Hb = haemoglobin, lab = laboratory, POC = point of care, diff = difference, SD = standard deviation, mean diff = mean difference, count = number of patients, AKI = acute kidney injury and relative stage 0 represents no AKI, stage 1, 2 or 3, Hb units is g/L

8.7 Discussion

This study demonstrates that there is a place for the clinical application of POC testing in real-world sampling contexts. As with previous studies[5,13,14] we have found that blood gas analyses can compare well against the gold standard laboratory result. POC results are interpreted within clinical context, often with closer chronological association than laboratory tests, rather than as absolute numbers in isolation. Therefore, these results are highly suggestive that management could be justifiably altered and could bring significant reduction of time between result and action. The reliability of a result being normal, low or high in conjunction with a supportive clinical backdrop should be grounds to initiate action.[1]

Given the speed at which a POC test can be taken, processed and returned by either the clinician or member of the multidisciplinary team, POC testing has clear advantages over laboratory sampling. Not only is the POC test usually timely and performed in an immediate clinical context, but it is also usually interpreted by the same individual involved in the care of that patient who can then initiate or alter management immediately. The delays in taking, delivering and processing laboratory samples, which then may be handed over or checked *en masse* by a junior team creates a dissonant relationship between the clinical scenario and a the response time to initiating action.

Across clinical contexts, POC testing as a whole still lacks adequate governance in terms responsibility and accountability and, while there is a strong demand for rapid tests and digital advances, these must come with internal quality control structures and external quality assurance and evaluation.[15]

Overall POC testing performs particularly well when values lie within normal ranges. This was true for potassium, sodium and haemoglobin where in these cases an excellent correlation with laboratory values was often seen. This is reassuring,

given the limitations of this study and the real-world sampling that this data is derived from.

8.7.1 Potassium

POC testing in potassium was most accurate in the normal range. More often than not, lower POC potassium results were in fact normal. Therefore, treatment for hypokalaemia would not be indicated unless greater than 1 mmol/L beyond the usual treatment threshold, unless clinically indicated otherwise, for example in arrhythmias, where clinicians may wish to aim for a potassium of 4.0mmol/L; or where a finding of hyperkalaemia from the POC testing is accompanied by supportive ECG findings.

Clinically this is of particular use in patients with unexpected hyperkalemia in a community setting. An urgent repeat of the potassium result with POC testing could support rapid turnaround and discharge from the ED, or a change in management such as cessation of hyperkalaemia treatment or hypokalaemia treatment. This is relevant for patient flow, safe discharge and the effective use of cardiac monitoring.

8.7.2 Sodium

POC sodium testing showed that low to normal sodium results 125-145mmol/L were well correlated and accurate in comparison to the laboratory values. The mean sodium value at 136.9mmol/L is at the lower end of normal, and reflects the sick hospital population; however, in an ageing population it may also be necessary to reconsider the normal value range ‘normogram’, as our study demonstrates that 131.9mmol/L is 1 SD below the mean, yet still considered low.

Low sodium on POC was more likely to be correct in those with AKI 3 rather than dialysis, UTI rather than COPD, and younger patients. This is an observational study and cannot determine causality. There was an increasing range of sodium results seen as AKI stage increased, which probably reflects the significant alteration in fluid balance seen in patients who suffer AKI.

This study suggests that POC testing is unlikely to be sufficiently accurate to monitor cases of severe hyponatraemia correction as the error margin may be too great at lower ends of the spectrum, but with standardised sampling, identical machine use and clinical judgment it could be used as a guide.

8.7.3 Haemoglobin

POC tests were most reliable in the normal range. In particular, only 2.5% of patients would have a low laboratory haemoglobin if the POC result was normal. This result is very reassuring and could allow safe discharge, or support decisions to await other investigations rather than proceed to transfusion with its attendant risks. Likewise, as the standard deviation is 10 g/L, transfusion in the context of suspected bleeding, or of anaemia below the local transfusion threshold in patients with or without ischaemic heart disease, would be supported prior to receiving formal laboratory results.

8.8 Limitations

There are some limitations with this study that require careful consideration, and could limit the widespread application of the findings. It was not possible to compare quality control testing and assurance timings with samples against both POC and laboratory machines. Also these results are only applicable to this combination of POC and laboratory machines and their calibration settings. Individual combinations of analysers will need to be checked for concordance before these results could be widely generalizable.

Some samples were censored where they did not have a correlating sample (either POC result or laboratory result) with 1 hour. We were also unable to compare emergency samples if the patient ID was not known or not entered correctly as this does not register to any registered patient details. It cannot be known whether samples drawn within the 1-hour window may have been drawn post treatment, for example, to monitor the effect on potassium after hyperkalaemia treatment.

There may be sample drawing variability as either the POC or laboratory blood test could be direct samples through a vacutainer, syringe or taken through a newly inserted cannula. This may lead to a differing risk of haemolysis that can adversely affect potassium. As these are real world samples it is likely that there will be some human error in the sampling process such as drawing blood from a “drip arm” and therefore diluted or contaminated which cannot be fully corrected for in the statistical process.

8.9 Conclusion

This study provides significant data with regards to real-world application of previous smaller studies. It uses acute unselected admissions and compares values from 'front door' POC tests with those from the laboratory. As with previous studies, it suggests the majority of the out-of-range POC values cannot be used interchangeably in isolation; however, the normal-range values have a good level of accuracy and corroboration to give clinically meaningful results. This could feasibly lead to faster management initiation or alteration, and should be addressed and included by policy makers, and serve to inform future POC use. Further evaluation of POC testing management could lead to improved accuracy, greater test fidelity and positive influences upon the further development of POC tests.

8.10 References

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Chapter 9.

Evaluation and future directions

9.1 Rationale

This final chapter critically evaluates the preceding chapters of this thesis. It will discuss key themes and outline how the results will lead to future investigations and inform further projects.

9.2 Introduction

This PhD has delivered six results chapters that explore acute kidney injury (AKI) and its management in more detail than is described in the current literature. By using 'big data' it has begun exploring the heterogeneity of AKI episodes and the risks of AKI in the contexts of different conditions, and looked to address these through a quality improvement project.[1] It is clear from the completed work that AKI is associated with critical care admission and mortality and through the quality improvement work and AKI app we sought to attenuate and address some of the complications that are associated with AKI.

The data has been made possible by the digital maturity at this hospital site. The wealth of research that has been possible is a strong argument in favour of similar advances and use of data elsewhere to not only validate this research in different hospital settings and within different community populations, but also to fuel further work. On the national stage this would support efforts to lobby for better integration of computer systems and the creation of unified NHS shared software and a pathology lab spine to allow higher quality, integrated and impactful research.

9.3 Evaluation

9.3.1 Evaluation of Chapter 1: A narrative review of the impact of interventions in acute kidney injury[2]

The literature review appraised the current evidence for impact on measured outcomes (mortality, renal morbidity, change in creatinine, dialysis, AKI progression, AKI incidence) through a variety of methods: the AKI bundle, AKI nurses, the AKI e-alert, sick day rules, education packages and AKI apps.

The review complemented the initiation of the work done in the AKI quality improvement project in Chapter 6[1] and informed the collaborative group as to the current evidence base for effective strategies. Overall it was clear that a combination of AKI e-alert with AKI bundle, multidisciplinary team education and an inbuilt redundancy in the system were the key constituents of successful projects and of statistically significant outcomes for patient mortality, dialysis incidence and critical care admission. This literature review highlighted key areas of focus that were explored in Chapter 6, the AKI collaborative, and Chapter 7, the AKI Care app.[1,3] There are other areas of research prompted by this work, such as the transitions of care between primary and secondary care areas, and further work on risk stratification, that are picked up in section 9.3 ('future work').

As yet there are no published initiatives that show significant improvement in AKI outcomes. This requires work across primary care and hospital systems to both identify and actively manage the highest-risk patients. Generic sick day rules have struggled to gain traction and lack evidence; therefore a return towards personalized care, and robust care systems with early escalation for senior clinical review, may comprise a more effective strategy.

Since this research and publication of this chapter, further work has been completed and published on both quality improvement projects and AKI risk evaluation. A step-wedged cluster design over four sites for an AKI bundle of interventions showed a reduced length of stay but no significant change in mortality.[4] The ICE-AKI study showed a mortality reduction (OR 0.99, 95% CI 0.98-1.00, p=0.049) in patients with hospital-acquired AKI through the development of a risk prediction tool, instigating the activation of an AKI bundle and the notification of an outreach nurse.[5] They saw no improvement in length of stay or community acquired AKI. The

'RISK' study was performed across UK acute medical units, showed only a moderate discriminatory value to their AKI risk prediction model and therefore could not recommend widespread use.[6]

The latest work from Deepmind's collaboration with the Royal Free Hospital in London ties in with Chapter 7, the AKI care app. The development of their mobile app 'Streams' has led to the correct prediction of 55.8% of all episodes of AKI and 90.2% of all dialysis-requiring AKI.[7] This is only within a limited male population and is yet to be tested in a more diverse population. It holds some new promise for detecting AKI up to 48 hours earlier, however with a false positive rate of two to one, there is a risk of alert fatigue. The detection rate of 55.8% runs the risk of being overhyped given the artificial intelligence connection. The next steps are to test in a representative cohort and then enact interventions to assess whether there are meaningful improvements in care that can reduce AKI incidence, progression or severity, with hard end points such as mortality, dialysis incidence and critical care admission.

9.3.2 Evaluation of Chapter 2: Generic Methodology

The generic methodology chapter describes broad concepts for consideration and context when evaluating this work. It highlights the patient population this work is based upon, and therefore its generalisability. Validation of this work in other populations with different ethnicities, different tertiary service provision, or in district general or primary care settings could ensure this work is widely applicable.

9.3.3 Evaluation of Chapter 3: Comparison of impact on death and critical care admission of acute kidney injury between common medical and surgical diagnoses[8]

This manuscript identified several important aspects of AKI care. We should consider how different clinical environments and processes might predispose or protect from AKI, we should also assess external inequalities in care in terms of access to intensive care or to senior clinical decision-makers. Exploration of this with quality improvement methodology is key to evaluating and understanding some of the observed differences in patient outcomes.

AKI should be included in the policy documents that cover safety of patient transfer and of outlying patients (the practice of bedding patients on wards where their parent team is not based to deal with bed pressures). Patients with any AKI, either community- or hospital-acquired, should not be considered sufficiently medically stable to outlie, nor should they be deemed suitable for discharge until resolution or stability appears likely, and has been reviewed by a senior clinical decision maker.

9.3.4 Evaluation of Chapter 4: The effect of AKI stage on mortality in different admission diagnoses: is AKI 2 comparable to AKI 3?

Little research has been done into the differing effect of AKI stage 2 compared to AKI stage 3, and this chapter sought to add knowledge to this complex area. This chapter demonstrated that mortality in these more severe stages of AKI could follow different patterns depending on admission diagnosis. There were several groups that followed a linear pattern of increasing mortality with increasing AKI stage. However, the cardiovascular groups plateaued, with AKI stage 2 and 3 having similar mortality risk. Patients admitted with fracture neck of femur had an exponential rise in mortality risk with AKI 3.

As in chapter 3, the phenotype of the different groups, although adjusted for in the statistical analysis, will continue to have some bearing on outcomes. It is important to acknowledge that frailty and comorbidity are not easily adjusted for in our model of analysis. Our next research project intends to assess the risk in these groups of cardiovascular patients and tries to elucidate whether pre-existing chronic kidney disease (CKD), AKI, or AKI on CKD is the biggest contributor to mortality.

9.3.5 Evaluation of Chapter 5: The influence of multiple episodes of acute kidney injury on survival and progression to end stage kidney disease in patients with chronic kidney disease[9]

This chapter focused on patients with pre-existing CKD and looked at the effect of multiple episodes of AKI. The chapter looked at risk factors for multiple episodes of AKI as well as AKI severity in a more focused population with a pre-existing risk factor for AKI, i.e. the presence of CKD. There were limitations: the cause of AKI could not be widely ascertained and therefore was excluded (however, due to the

relatively small numbers in the analysis it is unlikely that this would have significantly affected the results). Likewise, as in each of the other chapters, urine output was not available for analysis in the extended KDIGO AKI staging criteria.[10] This is a recurrent limitation on busy acute medical wards and research has failed to come up with a robust system for fluid balance measurements in uncatheterised patients outside of the intensive care setting.

9.3.6 Evaluation of Chapter 6: Reducing acute kidney injury incidence and progression in a large teaching hospital[1]

Within the AKI community it is clear that we have moved on from monitoring the crude number of e-alerts to monitoring their effect within systems through an AKI bundle. The QI work (Chapter 6) clearly shows that an AKI alert should reliably trigger a tangible set of evidence-based actions, drawn from the initial literature review. Reliable use of AKI bundles, education and an in-built redundancy or safety net results in fewer hospital-acquired AKIs and fewer instances of progression to severe AKI. Other closely related-research also demonstrates that this approach can lead to fewer AKI days, reduced length of stay and improved mortality.[4,11,12] Learning from these different initiatives could lead to fewer complications, less need for dialysis and significant cost savings, which is important, given that managing AKI in the UK costs £1 billion per year, 2% of the NHS budget.[13]

AKI is an illness barometer and may reflect not only patient care and safety within specific clinical environments, but also the robustness of processes of care within departments. This research would therefore support considering in-hospital AKI 3 as a 'serious untoward event' or similar. Whether this is through formal adverse incident reporting or remote audit sampling, the severity of outcomes in patients with AKI 3 justifies looking at the root cause for these for thematic analysis.

9.3.7 Evaluation of Chapter 7: The "AKI care app": live clinical decision support or reference tool[3]

This chapter evaluated the 'AKI care app', a software application that was developed prior to the AKI e-alert. It has a straightforward user interface and helps users to calculate AKI stages, presence or absence of complications and signposts to onward

referral. It was quickly superseded by the AKI e-alert and then became more of an education and reference tool. The vast numbers of entries that were unlikely to be compatible with life suggested that users were exploring the functionality of the app rather than entering real-life clinical biochemical parameters. As mobile phones have become ubiquitous, integration of mobile use at the bedside has become a routine practice. However, this is limited by battery life, network coverage and 'bring your own device' policies in hospitals. Both user and patient acceptability is yet to be explored and there is some evidence to suggest that interactive technologies can lead to alert fatigue and reduce the quality of face-to-face communication in patient interaction.

9.3.8 Evaluation of Chapter 8: A comparison of point of care testing with gold standard laboratory testing in different clinical settings

With the advent of point of care (POC) testing it is crucial to not only understand their correlation with gold standard laboratory equivalents but also their clinical applications. Currently, guidance does not support the replacement of gold standard laboratory investigations with POC testing results. Current literature suggests caution in using laboratory and POC testing interchangeably in real-world settings outside of controlled research environments. However, the results here suggest that normal values outputted from POC testing are reliable and can be used, with clinical judgment, in a meaningful and effective way to affect patient management decisions, appropriate use of monitoring and patient flow. There will be several quality-control and quality improvement measures that need to be undertaken prior to widespread generalization of these actions. However this research indicates that point of care testing could be much more effectively used and incorporated into policy-making than it is at present.

9.4 Future work

In order to address prevention there must be a collaborative approach to work spanning primary into secondary care and vice versa. More rapid transitions of care *from* the community for investigation and back *out* into the community for monitoring rely on rapid, accurate and effective communication.

The surviving sepsis campaign has garnered great success as a result of thoughtful social media and public relations work, and AKI strategists would do well to learn from and collaborate with colleagues from that campaign, as sepsis is such a significant cause of, and association with, AKI.[14,15] Likewise AKI should be addressed as part of the National Early Warning Score system (NEWS 2) in order that NEWS 2 can reflect the haemodynamic instability of patients. This would support nursing colleagues and junior doctors to escalate patients to more senior clinical decision makers for advice and review of management in an effective way. [16] There is also scope to focus on targeted in-hospital populations, probably following thematic analysis of stage 3 AKIs. It is highly likely that, by selecting high incidence, high mortality AKI 3 patient populations, deficiencies in care or processes may be identified early and through formal feedback, education and training in order that further similar incidents could be avoided.

Similarly, point of care creatinine testing ought to be considered alongside the POC testing addressed in Chapter 8. POC creatinine may provide greater and more detailed data about AKI in the community and AKI recovery post discharge from hospital. It may provide safer monitoring for patients with ACE inhibitor initiation, recurrence of primary renal disease such as vasculitis, or else aid in sepsis severity stratification. It is yet to find its niche in the community setting, however: cost efficiency may score in its favour for outpatient clinic settings for stable CKD monitoring, or even for prognostication for those on conservative care pathway trajectories. Rather than full biochemistry profiles, more frequent monitoring would allow clinicians to see creatinine results in clinic with real-time advice, rather than delayed review of the blood tests after clinic with dictation or amendment of a clinic letter with advice. This could be useful to highlight to patients with CKD and recurrent AKI of their trajectory towards renal replacement therapy.

So far there has been little progress on AKI risk assessment in the generalized population. Given the results this PhD has generated, perhaps looking towards big datasets and narrowing in on specific populations would be a fruitful strategy in this regard. It is likely that patients who develop AKI may well have composite risk factors for further episodes of AKI. It would seem pertinent to treat more severe episodes in particular with follow-up, and to develop strategies for secondary prevention in a similar way to that used for cardiovascular events. These measures

could be patient-specific, such as tailored fluid balance and ‘sick day’ guidance for medication or rapid access to point of care creatinine testing with early senior review.

With the advent and augmentation of technology it is important to be ever mindful of alert fatigue. Unnecessary, inappropriate or overly frequent interruptive alerts can lead to alert fatigue and workarounds by users. Judicious use of forcing functions, to mandate interaction with the alert, education as to the importance of the alert and appropriate staffing and resources to react to the alert are key to maintaining appropriate and timely response.

9.5 Conclusion

AKI is benefiting from significant attention, not only from within the renal specialty but also from acute medicine and intensive care specialists. It is paramount that this interest is capitalized upon to maintain the momentum and enthusiasm for AKI research and make the most of potential funding opportunities.

This PhD in particular highlights that there are potential targets that could significantly reduce AKI days, hospital-acquired AKI incidence and therefore potentially reduce progression of or into CKD or patient mortality. This work gives insight into the heterogeneity of AKI episodes and will guide further evaluation and research into the epidemiology and phenotype of patients at risk of all stages of AKI. Considering AKI as an illness barometer and considering AKI to be everybody’s problem will improve standards of care and outcomes for patients. Through assessing risk and individualizing patient’s care, we can achieve meaningful differences in AKI acquisition and progression.

9.6 References

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Appendix

Publications and abstracts arising from this thesis

A1 Publications included in this thesis

"A narrative review of the impact of interventions on acute kidney injury"
Sykes L, Nipah R, Kalra P, Green D. J Nephrol. 2017 Nov 29,
DOI: 10.1007/s40620-017-0454-2

"So044 The Introduction Of A Novel Smartphone App To Tackle Acute Kidney Injury In North West England"
Sykes, L , Richie, J, May 2017, NDT 32(suppl_3):iii27-iii27,
DOI 10.1093/ndt/gfx107.SO044

"Reducing acute kidney injury occurrence and progression in a large teaching hospital"
Sykes L, Sinha S, Hegarty J et al BMJ Open Qual 2018;7:e000308.
DOI: 10.1136/bmjoq-2017-00308

"Comparison of impact on death and critical care admission of acute kidney injury between common medical and surgical diagnoses"
Lynne Sykes, Philip A. Kalra, Darren Green, PLOS ONE 2019
DOI: 10.1371/journal.pone.0215105

"The influence of multiple episodes of acute kidney injury on survival and progression to end stage kidney disease in patients with chronic kidney disease"
Lynne F Sykes, Ozgur Asar, James P Ritchie, Maharajan Raman, Diana Vassallo, Helen V Alderson, Donal J O'Donoghue, Darren Green, Peter J Diggle, Philip A Kalra, PLOS ONE 2019 Jul 18;14(7):e0219828.
DOI: 10.1371/journal.pone.0219828

A2 Related publications not in this thesis

“Sp833 Evaluating Pharmacist Medication Interventions In Emergency Admissions With Community Acquired Acute Kidney Injury In A Large Teaching Hospital” **Sykes L**, Reed A, Lamerton L, May 2017, NDT 32(suppl_3):iii423-iii424, DOI: 10.1093/ndt/gfx159.SP833

A3 Publications submitted to journals pending decisions

"Examining the implementation of clinical decision support systems to improve patient safety: an ethnographic study of acute kidney injury in secondary care" Simon Bailey, Carianne Hunt, Adam Brisley, Susan Howard, **Lynne Sykes**, Tom Blakeman
Submited to BMJ Quality and Safety: accepted with revisions

A4 Abstracts presented at international meetings

ASN, American Society of Nephrology, 17th November 2016, Chicago "A Novel Quality Improvement Project to Reduce Acute Kidney Injury in a Large Teaching Hospital" (oral presentation)

ERA, European Renal Association, 4th June 2017, Madrid "The Introduction of a novel smartphone app to tackle acute kidney injury in North West England" International Society of Nephrology teleconference to sister hospital in Nigeria on the topic of AKI 25th October 2017 (**oral presentation**)

ERA, European Renal Association, 3-6th June 2017, Madrid "Evaluating Pharmacist Medication Interventions in Emergency Admissions with Community Acquired Acute Kidney Injury in a Large teaching hospital" (poster presentation)

SAM, Society of acute medicine, 4th May 2018, Amsterdam “The impact of AKI in acute medical admissions” (oral and poster presentations)

ERA, European Renal Association, 14th June 2019, Budapest “The influence of multiple episodes of acute kidney injury on survival and progression to end stage kidney disease in patients with chronic kidney disease” (**oral presentation**)

A5 Abstracts presented at National meetings

BMJ and International Health Institute (IHI) International Forum on Quality and Safety in Healthcare, 27th April 2017, London "A Novel Quality Improvement Project in Acute Kidney Injury in a Teaching Hospital: Second Phase" (poster presentation)

HRSUK Health research and science UK, 6-7th July 2017, Nottingham "Understanding context in quality improvement: Ethnographic hospital case studies of AKI improvement initiatives" (poster presentation)

AKI Frontiers, Royal Society of Medicine, London, 10th October 2018 “An update on the AKI collaborative” (**oral presentation**)

A6 Related prestige as a direct result of this thesis

UKKW UK Kidney Week, 19th -21st June 2017, Liverpool - Chair of AKI session

UKKW, UK Kidney Week, 19-21st June 2018, Harrogate – Chair of AKI session

HSRUK Health research and science UK, 4-5th July 2018, Nottingham – Panel for “Current directions and dilemmas for ethnography in healthcare improvement research”

AKI Frontiers, Royal Society of Medicine, 10th October 2018, London – Chair and invited speaker

UKKW, UK Kidney Week, 3-5th June 2019, Brighton - **invited speaker** on AKI and multimorbidity

A7 Grants and bursaries

ERA, European Renal Association, 13-16th June 2019 Budapest travel grant (€500)

A8 Prizes and awards

UKKW, UK Kidney Week, 7-10th June 2016, Birmingham - best poster presentation prize winner "Acute Kidney Injury: A Quality Improvement Approach"

Finalist of Quality Improvement Project of the Year, Leicester, 30th November 2016 "A Novel Quality Improvement Collaborative to Reduce Acute Kidney Injury Incidence and Progression in a Large Teaching Hospital"

Finalist HSJ, Health Sciences Journal, Patient Safety Awards July 2017 "Acute Kidney Injury Collaborative"

ERA, European Renal Association, 13-16th June 2019, Budapest “Best abstract winner”