Predicting Acute Kidney Injury

PhD Thesis

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Abstract

The overarching aim of this PhD thesis is to develop methods, which will ultimately improve the management of patients with acute kidney injury (AKI). Over the years one inherent problem in both diagnosing AKI clinically and reviewing and comparing studies published in the literature has been the numerous definitions used to define AKI. [87] With now accepted definitions of AKI, the first question raised was to determine the true impact of AKI, in terms of incidence and outcomes, for both the patient (morbidity and mortality) and the healthcare economy.

A retrospective observational database study was performed from secondary care in East Kent (adult catchment population of 582,300). All adult patients (18 years or over) admitted between 1st February 2009 and 31st July 2009, were included. Patients receiving chronic renal replacement therapy (RRT), maternity and day case admissions were excluded. AKI was defined by the acute kidney injury network (AKIN) criteria. A time dependent risk analysis with logistic regression and Cox regression was used for the analysis of in-hospital mortality and survival.

The incidence of AKI in the 6 month period was 15,325 pmp/yr (adults) (69% AKIN1, 18% AKIN2 and 13% AKIN3). In-hospital mortality, length of stay and ITU utilisation all increased with severity of AKI. Patients with AKI had an increase in care on discharge and an increase in hospital readmission within 30 days. In comparison with patients with no AKI those with AKI stage 1 had a 52% longer length of stay (LOS) in hospital, a 2.8-fold increased risk of admission to the intensive therapy unit (ITU), a 39% longer ITU stay (in those who went to ITU), and a 2.4-fold greater in-hospital mortality. Furthermore, patients with AKI stage 1 had twice the long-term risk of death, a 33% higher likelihood of an increase in care, and a 42% higher risk of re-admission within 30 days. In those patients with AKI stage 3 (the subject of the NCEPOD report) [100] hospital LOS

doubled, there was a 22 times higher risk of admission to ITU and ITU LOS was also doubled, consistent with national data from the Intensive Care National Audit and Research Centre.

A further study using this data in collaboration with Marion Kerr (health economist) at the Department of Health, suggested the annual number of excess inpatient deaths, with AKI in England may be greater than 40,000, [106] and the annual cost of AKI-related inpatient care in England is estimated at £1.02 billion. [106]

With the problem now evident and clearly defined, the first stage in improving management was to alert clinicians to the presence of AKI as soon as possible to allow early recognition and intervention. Here the development of a static AKI alert report delivered to the critical care outreach team and specialist renal team is documented.

A qualitative analysis was then used to explore the effect of professional interactions, information sharing, and personal and professional characteristics on the use of electronic clinical information and clinical decision support. Key areas highlighted in the qualitative analysis included real-time delivery of AKI alerts, clear responsibility of care to be with the clinical teams with advice from the critical care outreach nurses and renal consultants as required, and improved communication with the clinical teams looking after the patients. This work informed a development partnership with a commercial company (Careflow Connect Limited) to deliver real-time alerting of acute kidney injury to clinicians at the point of care and allow collaboration within the clinical team and also with the specialist renal and critical care outreach teams.

However, in any disease process, while we can optimise our measures in place (as above) to alert to the presence of a disease (in this case acute kidney injury (AKI)) and manage it effectively and efficiently at recognition, the ultimate form of treatment is the prevention of the disease occurring in the first place. Hence, in order to achieve this we need to determine the patient at risk.

Firstly, potential risk factors were explored. Three time points were also defined where significant clinical decision making takes place and at which points the use of risk models would have greatest impact on clinical care and patient management. These were the point of admission to hospital to guide renal function testing and inform admission planning, and secondly, at 24 hours after admission, often on the post-take ward round to highlight patients who are likely to develop new or worsening AKI if already present, in the first 72 hours of hospital admission so that appropriate management decisions can be made on the ward round.

The study population included hospital admissions to the three acute hospitals of East Kent Hospitals University NHS Foundation Trust (EKHUFT) in 2011, excluding maternity and elective admissions. For validation in a second population the study included hospital admissions to Medway NHS Foundation Trust.

The study developed and assessed traditional methods to provide risk models for the prediction of new or worsening AKI in patients presenting to hospital and in their management within the first 24 hours of admission. Ordinal logistic regression with uni-variable analyses were used to inform the development of multi-variable analyses. Backward selection was used to retain only statistically significant variables in the final models. The models were validated using actual and predicted probabilities, Area Under the Receiver Operating Characteristic (AUROC) curve analysis and the Hosmer Lemeshow test.

The analysis identified key variables which predict AKI both at admission and 72 hours post admission. Validation demonstrated area under ROC of 0.75 and 0.68 respectively. Predicting worsening AKI during admission was unsuccessful.
These models were also re-defined with use of the NHS England algorithm to define AKI which produced similar results with area under ROC of 0.73 and 0.67 respectively.

The work reported here has demonstrated the significant morbidity and mortality both long and short term of patients who experience acute kidney injury managed in hospital and has developed methods of alerting the presence of AKI to the point of care in real-time to ensure efficient intervention with an aim to improve these outcomes. Qualitative work has also highlighted the complexity regarding the implementation and delivery of alerting systems to the clinical front line. The work reported in this thesis has also demonstrated that routinely available data can be used to highlight patients at risk of acute kidney injury both at the point of admission to hospital and following admission.

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List of Abbreviations

A&E	accident and emergency
ACKD	acute-on-chronic kidney disease
AKD	acute kidney diseases and disorders
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ALT	alanine transaminase
AMY	amylase
ATN	acute tubular necrosis
AUC	area under the curve
AUROC	area under the receiver operating characteristic
BNP	brain natriuretic peptide
CDSS	clinical decision support system
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
CSU	catheter specimen urine
eGFR	estimated glomerular filtration rate
EKHUFT	East Kent Hospitals University NHS Foundation Trust
ESRD	end-stage renal disease
HbA_{1c}	glycated haemoglobin
ICD-10	International Classification of Diseases, Tenth Edition
ICU	intensive care unit
ITU	intensive therapy unit

KDIGO	Kidney Disease: Improving Global Outcomes
MDRD	modification of diet in renal disease
MSU	mid-stream specimen urine
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
PLT	platelets
RIFLE	Risk, Injury, Failure, Loss of function, and End-stage renal failure classification
ROC	receiver operating characteristic
RRT	renal replacement therapy
SHO	senior house officer

Acknowledgements

I am grateful to the Department of Renal Medicine, East Kent Hospitals University NHS Foundation Trust (EKHUFT) where this work was performed.

Mr Toby Wheeler, IT Application Manager, and the staff in the Department of Information at EKHUFT, for assistance with data extraction and programming of the acute kidney injury (AKI) detection algorithm.

Dr Sanjay Suman (Consultant Physician and AKI Clinical Lead for Medway NHS Foundation Trust) acted as the liaison with Medway to facilitate data extraction for our second population for validation of the risk models. Mr Brian Hughes (Business Intelligence Manager at Medway NHS Foundation Trust) provided the data extraction for the second population at Medway.

I also wish to thank other members of the Kent Kidney Research Group for their support and advice in design and delivery of these studies. In particular, the support of Dr Paul Stevens (Consultant Renal Physician and Medical Director EKHUFT) and Mrs Helen Hobbs (Senior Research Nurse).

I would like to thank Mr Paul Bassett (Statistician, Statsconsultancy Limited) for help and support with statistical analysis.

I would like to thank my supervisors Professor Chris Farmer and Professor Simon Coulton for their support and guidance, and the support of the Centre for Health Services Studies (CHSS) at the University of Kent.

I acknowledge the support of the National Institute for Health Research (NIHR) through the Health Services and Delivery Research (HS&DR) programme (Grant Reference 11/2004/28).

Declaration

This work has led to the publication of 4 peer reviewed journal article publications with myself as the first author in three of these (see Appendices 1-4), and the publication of the National Institute for Health Research (NIHR) – Health Service and Delivery Research (HS&DR) study 11/2004/28 report (Appendix 8) of which I was first author.

The introductory literature review (Chapter 1; published paper Appendix 1) was performed by myself with critical review and guidance by Professor Chris Farmer, Dr Paul Stevens and Dr Tariq Ali at EKHUFT and Dr Adeera Levin from the University of British Columbia, Vancouver, Canada.

In the study to define the epidemiology of acute kidney injury (AKI) (Chapter 2; published paper Appendix 2), design of the study, definition of the dataset and data point determination from the databases was performed by myself. The data was extracted by Mr Toby Wheeler (IT Application Manager, EKHUFT). The data was cleaned by myself and anonymised. The algorithm for detecting AKI was defined by myself and programmed and run on the dataset by Mr Toby Wheeler. Stata (verion 12.1) was used for statistical analysis. The use of Stata was performed by Mr Paul Bassett (Statsconsultancy Limited), with variable selection, data interpretation and method determined by myself in collaboration with Mr Paul Bassett. The peer reviewed publication (Appendix 2) was written by myself (first author) with critical review and advice from Dr Paul Stevens, Mr Toby Wheeler, and Professor Chris Farmer.

In collaboration with Mrs Marion Kerr (health economist) at the Department of Health, the data sources and analyses here were used to inform a health economic analysis of the short and long term impacts on quality of life and healthcare costs. As above, for the study of epidemiology, the design, definition of the dataset and data point determination from the databases was provided by myself. Data extraction at EKHUFT was provided by Mr Toby Wheeler. The data was cleaned and anonymised by myself. The Markov model was developed by

Mrs Marion Kerr with clinical advice and critique by myself, Professor Donal O'Donoghue (Consultant Renal Physician and honorary Professor of Renal Medicine at the University of Manchester) and Mrs Beverley Matthews (Director of NHS Kidney Care). The peer reviewed publication (Appendix 3) was written by Mrs Marion Kerr (as first author) with clinical advice and critical review by myself and Professor Donal O'Donoghue.

The development of static AKI alerting was designed and implemented (including training of critical care outreach nurses in the use of the system and management of AKI) by myself. The AKI detection algorithm was designed by myself. The automated software to detect AKI in the inpatient population was written by Mr Toby Wheeler, and the AKI report was designed by myself and developed by Mrs Jean Irving (Senior Developer, EKHUFT) and Mr Richard Ewins (Head of Information Development and Data Architecture, EKHUFT).

The qualitative analysis of use of the static alert system by the Renal Consultants and Critical Care Outreach Nurses was conceived and designed by myself in collaboration with Professor Jenny Billings (Professor of Applied Health Research, Centre for Health Services Studies (CHSS), University of Kent). The focus group and interviews were conducted by Professor Jenny Billings and the analysis performed by Professor Jenny Billings with advice from myself. I was not directly involved in conducting the focus groups and interviews as we believed this may bias the results. As above, I had implemented the AKI alert system, and trained the Renal Consultants and Critical Care Outreach Nurses in the use of the system and educated the Critical Care Outreach Nurses in the management of AKI. Therefore, if I was present at the focus groups or interviews this may have influenced the content as the participants may not have felt at ease or able within that setting to voice any concerns regarding the system.

In the next stage of development I, on behalf of EKHUFT, entered into a development partnership with Dr Jon Shaw and Dr Jonathan Bloor at Careflow Connect Limited, along with Professor Chris Farmer and Mr Toby Wheeler to develop real-time alerting to clinicians at the point of care and allow

collaboration within the clinical team, also involving specialist Renal and Critical Care Outreach teams. I had significant input in the design process of the clinical application in terms of clinical alerting, patient list functionality and SBAR handover and referral processes. This led to the Enhancing Innovation Through Collaboration Award from the Kent, Surrey and Sussex (KSS) Academic Health Science Network at their Expo and Awards 2016.

In the study to develop risk models for the prediction of AKI, the design and theoretical framework for the study, including obtaining funding from the NIHR HS&DR and project management of the study was performed by myself. Definition of the dataset including variable selection (with expert clinical advice from Professor Chris Farmer and Dr Paul Stevens) and data point determination from the databases was performed by myself. The data was extracted by Mr Toby Wheeler at EKHUFT and Mr Brian Hughes (Business Intelligence Manager) at Medway NHS Foundation Trust. The algorithm for detecting AKI was designed by myself in the first instance, and by NHS England in the repeat analysis and validation, and programmed and run on the dataset by Mr Toby Wheeler. Stata (version 12.1) was used for development of the risk models. The use of Stata was performed by Mr Paul Bassett (Statsconsultancy Limited) with variable selection, data interpretation and method determined by myself. This study, funded by the NIHR HS&DR programme was published in the peer reviewed NIHR Journals Library. This published report was written by myself (as first author), with critical review by Professor Chris Farmer.

Publications and Presentations Arising From This Work

Publications

Bedford M, Stevens P, Coulton S, Billings J, Farr M, Wheeler T, et al. Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission: a cohort and nested study. Health Serv Deliv Res 2016;4(6).

Bedford M, Farmer CK, Irving J, Stevens PE. Acute kidney injury: An acceptable risk of treatment with renin-angiotensin system blockade in primary care? *Can J Kidney Health Dis*. 2015;2:14-015-0044-y. eCollection 2015. doi: 10.1186/s40697-015-0044-y [doi].

Kerr M, **Bedford M**, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in england. *Nephrol Dial Transplant*. 2014;29(7):1362-1368. doi: 10.1093/ndt/gfu016 [doi].

Bedford M, Stevens PE, Wheeler T, Farmer CK. What is the real impact of acute kidney injury? BMC Nephrology 2014, 15:95 http://www.biomedcentral.com/1471-2369/15/95.

Bedford M, Farmer C, Levin A, Ali T, Stevens P. AKI and CKD: Chicken or Egg. Am J Kidney Dis. 2012;59(4):485-491

Abstract Presentations to Learned Societies

Bedford M, Wheeler T, Bloor J, Shaw J, Farmer C. Directing specialist care through alerting to mobile devices. Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Presented at: The King's Fund, International Digital Health and Care Congress, London, September 2014.

Bedford M, Wheeler T, Bloor J, Shaw J, Farmer C. Coordination of specialist care with clinical social networking. Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Presented at: The King's Fund, International Digital Health and Care Congress, London, September 2014.

Bedford M, Wheeler T, Stevens PE, Farmer CKT. Pre-operative ASA score independently predict post-operative acute kidney injury in an unselected surgical population. Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Presented at: 51st ERA / EDTA Conference, Amsterdam, June 2014.

Bedford M, Farmer CKT, Irving J, Stevens PE. Acute Kidney Injury (AKI): An Acceptable Risk of Treatment With ACE Inhibitors and Angiotensin Receptor Blockers? Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Presented at: British Renal Society, Manchester, May 2012.

Bedford M, Kilbride HS, Stevens PE, Ali TZ, Young A, Farmer CKT. Grass Roots Epidemiology: Acute Kidney Injury – How Common Is It And What Is Its Impact? Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Presented at: British Renal Society / Renal Association Conference, Birmingham, June 2011.

Abstract Poster Presentations

Kerr M, **Bedford M**, Matthews B, O'Donoghue D. The Economic Impact of Acute Kidney Injury in England. Poster at: American Society of Nephrology (ASN) Kidney Week 2013 Annual Meeting, Atlanta, November 2013.

Bedford M, Farmer CKT, Irving J, Stevens PE. Acute Kidney Injury (AKI): an Acceptable Risk of Treatment With ACE Inhibitors and Angiotensin Receptor Blockers? Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Poster at: ERA / EDTA Conference, Paris, May 2012.

Bedford M, Kilbride HS, Farmer CKT, Ali TZ, Young A, Stevens PE. Grass Roots Epidemiology: Acute Kidney Injury and Chronic Kidney Disease – Risk Multipliers. Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Poster at: British Renal Society / Renal Association Conference, Birmingham, June 2011.

Bedford M, Kilbride HS, Farmer CKT, Young A, Stevens PE, Ali TZ. Grass Roots Epidemiology: Acute Kidney Injury Network Classification and Outcomes Across All Spectrums of Acute Kidney Injury. Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust. Poster at: British Renal Society / Renal Association Conference, Birmingham, June 2011.

Thesis Aims and Introduction

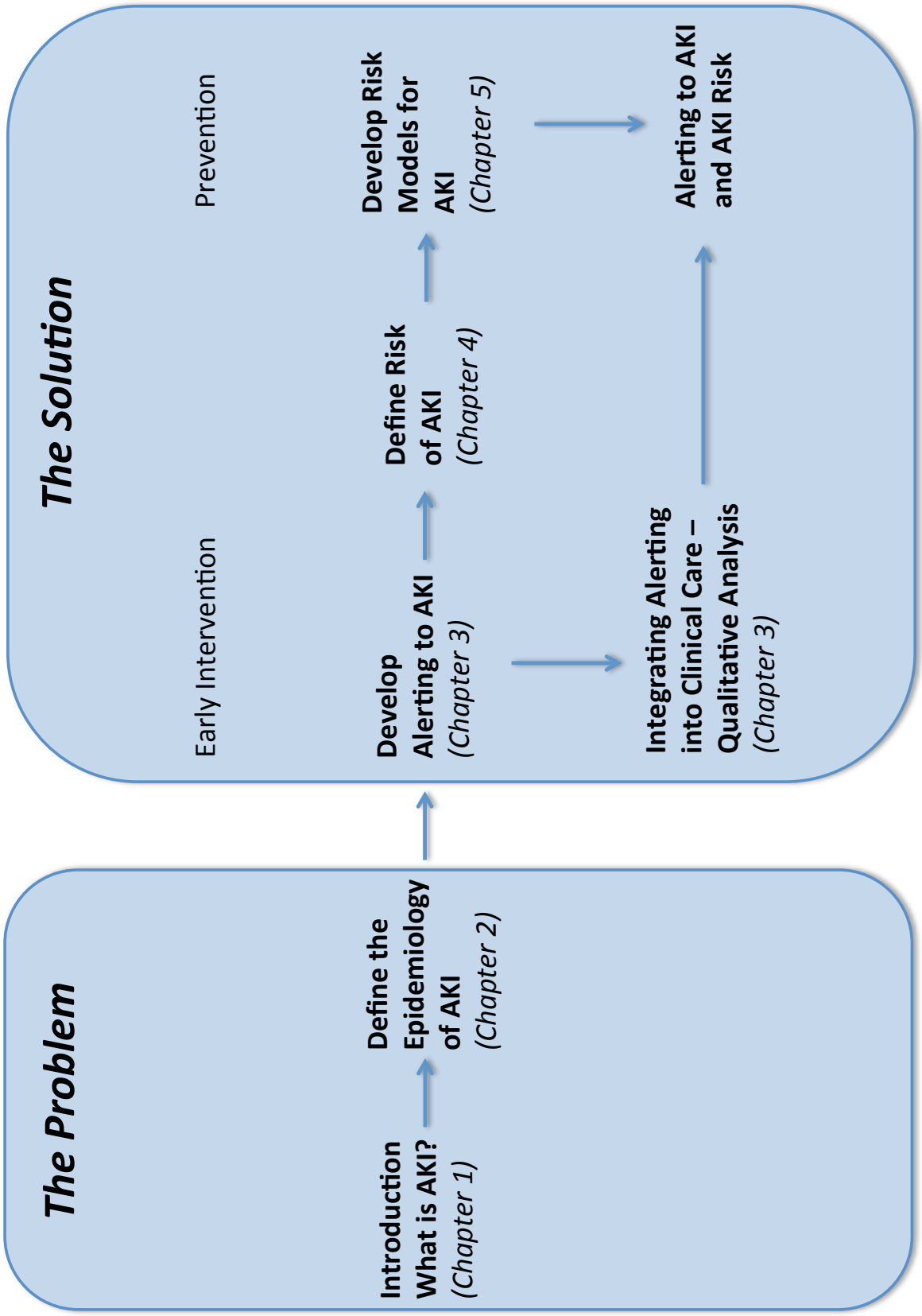
The overarching aim of this PhD thesis is to develop methods, which will ultimately improve the management of patients with acute kidney injury (AKI).

Following introduction (Chapter 1) of what defines AKI and what is already known about AKI from the literature, Chapter 2 will define the 'true' problem of AKI and set the scene as to why action is needed. Chapter 3 will develop and assess methods to provide AKI alerts to clinicians at the point of care to allow early recognition and early effective intervention in patients with AKI. As with any disease process however the ultimate form of treatment is prevention. Chapter 4 will introduce what is available in the literature in terms of known risk factors for AKI, and define the need for risk models to predict AKI in clinical practice. Chapter 5 will provide data on relationships between available variables / risk factors and AKI, and then modelling techniques will be used to provide a validated risk model and associated clinical algorithm to define patients at risk of acute kidney injury. Chapters 6 and 7 will conclude this thesis and define future work.

In short the aims and objectives of this PhD thesis are to:

1. Introduction – define acute kidney injury (AKI) and what is known from the literature (Chapter 1)
2. Define the 'true' epidemiology of AKI (Chapter 2)
3. Develop alerting of AKI to the point of care (Chapter 3)
4. Define risk of AKI – literature review (Chapter 4)
5. Develop risk models to predict AKI (Chapter 5)

Diagrammatic Thesis Plan



Chapter 1: Introduction

(Some of the work in this chapter is published in a peer review publication. See Appendix 1: Paper 1: Acute Kidney Injury and CKD: Chicken or Egg?)

Aims

The aim of this chapter is to set the scene of acute kidney injury (AKI) to document what is already known about AKI, how this knowledge base has developed over the years, and ultimately to develop research questions that will form the basis of this PhD thesis.

What is Acute Kidney Injury (AKI)?

Acute kidney injury (AKI), previously known as acute renal failure, is an all too common clinical problem characterised by an acute decline in renal function, the result of which ranges from minimal alteration in serum creatinine to anuric renal failure requiring renal replacement therapy (RRT). This abrupt rise in serum creatinine results from an insult or injury that causes a functional or structural change in the kidney. The aetiologies and risk factors for AKI are numerous, but now well defined. [1-4] Even without the need for RRT AKI may impact on a patient's clinical course with complications such as fluid overload, acidosis and hyperkalaemia, all of which may lead to an increase in morbidity, length of stay and ultimately mortality both long and short term. Renal outcomes include: full renal recovery, no renal recovery, development of chronic kidney disease (CKD) or progression of pre-existing CKD.[5-9]

AKI is increasingly well recognised as a public health issue and is both a consequence and a predictor of chronic kidney disease (CKD).[10-12] Its prevalence (4.9% amongst hospitalized patients in the USA) is increasing,[13] due to an aging population and the growing prevalence of the same risk factors contributing to the rise in CKD (including obesity, diabetes and hypertension), and also to better recognition.

Conceptual Model

The conceptual model of CKD is well established, and continues to inform clinical medicine, research and public health. [14-16] In contrast the concept of acute kidney diseases and disorders (AKD) is relatively new and attempts to map to the widely accepted CKD concept. The definition of AKI, in contradistinction to CKD, describes an abrupt, time-limited reduction of function, which has at least the potential to recover.

Both AKI and CKD describe decreased function, which can lead to complications including end stage renal disease (ESRD) and mortality. Risk factors for AKI and CKD are similar and there is a conceptual overlap and interplay between the two. AKI and CKD are both risk factors for each other, and also worsen the prognosis of each other. As acute kidney injury is discussed, the interaction and interplay between AKI and CKD must be kept in mind.

Underlying Biology

If the situation at a biological level is now considered, in the elderly CKD population, several factors could lead to increased susceptibility to AKI. Changes in the renal vasculature occur with age, just as in other vascular beds, often due to co-morbidity, but also in the absence of co-morbidity. [17] It is suggested these changes eventually cause cortical glomerulosclerosis, interstitial fibrosis and tubular atrophy, and compensatory hypertrophy and hyperfiltration of glomeruli in the medulla, contributing to development of CKD.[18] With increasing age and CKD, function in both proximal and distal tubules is compromised, hampering the ability to control fluid and electrolyte balance and affecting tubuloglomerular feedback. [17,19] These changes, related to age and CKD, may exacerbate clinical events such as dehydration and drug toxicity, which carry a high risk of AKI. [18]

Contrary to the idea that the diseased kidney is at increased risk of AKI, is the "intact nephron" hypothesis. [20,21] In surviving nephrons of a kidney with CKD,

there remains homogeneity of function and regulatory capacity. The kidney responds in a predictable and organised manner to maintain homeostasis in the face of a number of challenges. There may be less functional nephrons available, and reduced reserve, but available nephrons are functionally intact. This is evident until the late stages of disease and should therefore not produce an increased risk of AKI, but may impart an increased severity when it develops, which is therefore more likely to be clinically evident. There is also the concept of priming or conditioning, where the ischaemic or diseased kidney in CKD is more 'used to' insults and can therefore maintain function. This is somewhat at variance with epidemiological data (see below).

Given people with CKD have an increased burden of vascular disease, it may be that less of a vascular insult is required to provoke AKI. There are supportive data from animal models of AKI, which suggest AKI as a "vasomotor nephropathy" [22,23]. People with CKD and a greater burden of vascular disease may have increased severity of AKI when it develops, which is more likely to be clinically apparent and require hospitalisation, and thus be captured in epidemiological studies. Patients without CKD, and with less vascular disease, may have less severe AKI, manifest as 'silent and discrete' episodes in the community, and may not be captured in existing epidemiological studies suggesting an increased incidence of AKI in CKD.
Further prospective studies are required to assess the true incidence of AKI in patients with CKD, and correct more accurately for co-morbidity and hospitalisation.

But what happens following AKI? Renal tissue has the ability to recover from sub-lethal or lethal cellular damage. [24-27] However, function may not be fully restored, with development of CKD. [25] It is suggested kidney function can be directly related to a cycle of cell injury and recovery following AKI (Figure 1a). [28] This involves renal tubular epithelial cells, damage to which, is thought to be extended by renal vascular endothelial injury and dysfunction. It is believed that endothelial repair is important to overall renal recovery, and may impact on long-term function. [29] This model however considers acute tubular necrosis

(ATN) as the cause of AKI. What happens most frequently is limited to the very early part of this process. In patients developing CKD (Figure 1b) the initiating insult leading to damage, inflammation and repair (initiation) may result in fibrosis (extension) and then further damage in a self-perpetuating cycle of progression (maintenance) to end stage renal disease (ESRD). Early intervention at the stages of initiation and extension may prevent CKD and ESRD, whilst later intervention during the maintenance stage may only delay progression, the extent of delay determined by the success or otherwise of intervention. Patients with AKI may or may not have pre-existing CKD (Figure 1c).

Okusa *et al* (pathophysiological concepts from Sutton *et al*), suggest that following AKI, there are four possible outcomes: (1) full recovery, (2) incomplete recovery resulting in CKD, (3) exacerbation of pre-existing CKD accelerating progression to ESRD, and (4) non-recovery of function leading to ESRD. [28,30] (Figure 2) AKI may also incompletely recover leading to step down in GFR falling short of CKD. The fact that patients experiencing AKI are likely to also have risk factors for CKD, could suggest that patients without known background CKD who develop AKI already have unrecognised renal disease and reduced functional reserve, not yet manifest as CKD. These patients are programmed to develop future CKD, and the AKI episode simply speeds up development of overt CKD. In this respect, renal outcomes of AKI and CKD are the same, further evidence they are part of the same pathophysiological pathway.

A key question is whether the 'I' in AKI truly stands for injury or actually for impairment and/or injury? Is it under-pinned by histo-pathological damage, and if so, when does this become relevant in terms of future CKD or CKD progression? Do undetected episodes of AKI in the community lead to CKD? When patients present with CKD without an obvious cause, is the pathophysiology related to multiple undetected AKI events in the community?

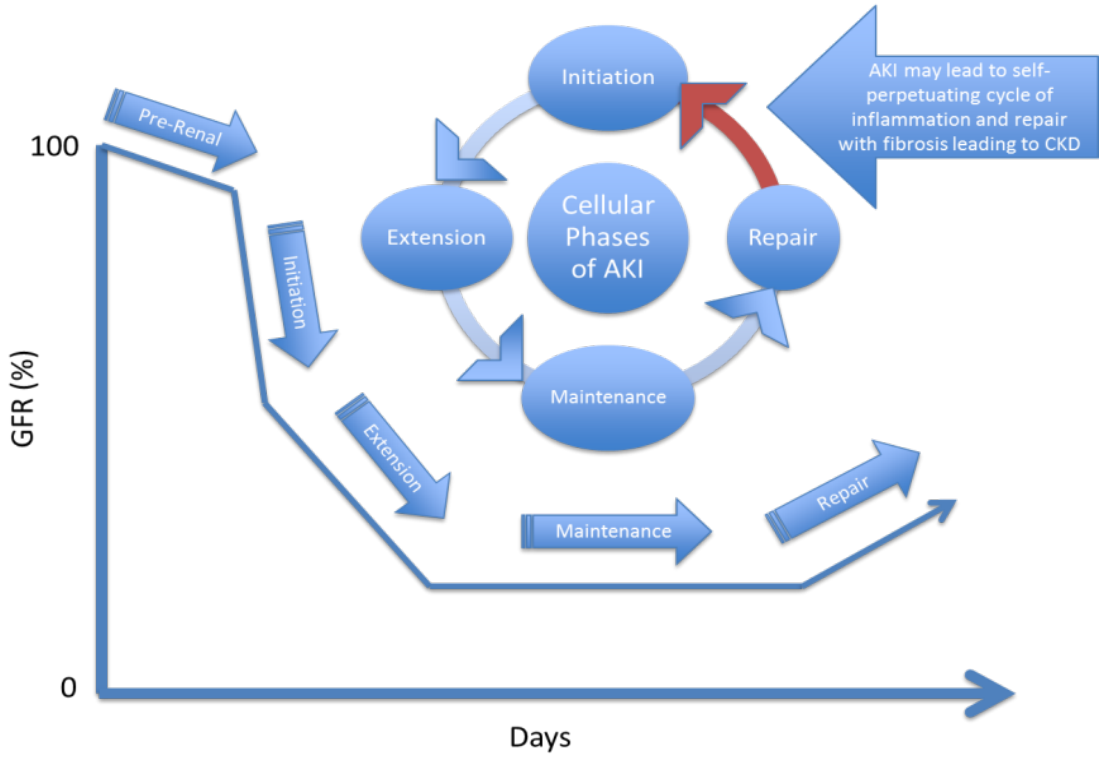


Figure 1a: Model of Acute Kidney Injury (AKI) over time

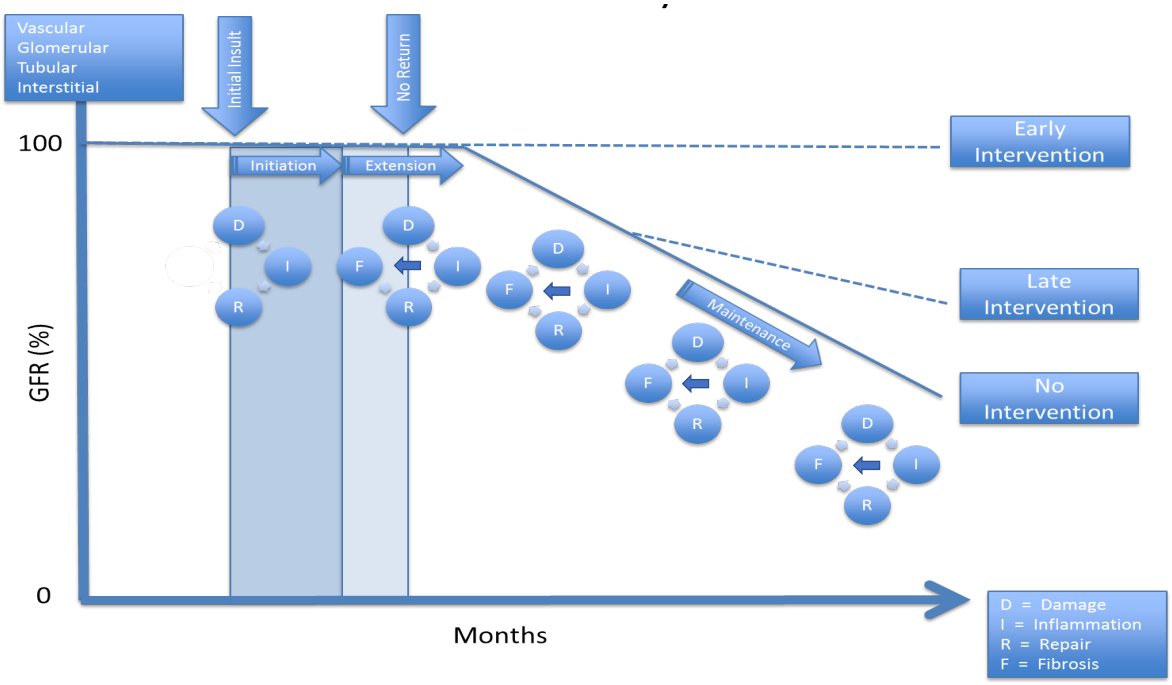


Figure 1b: Model of Chronic Kidney Disease (CKD) over time

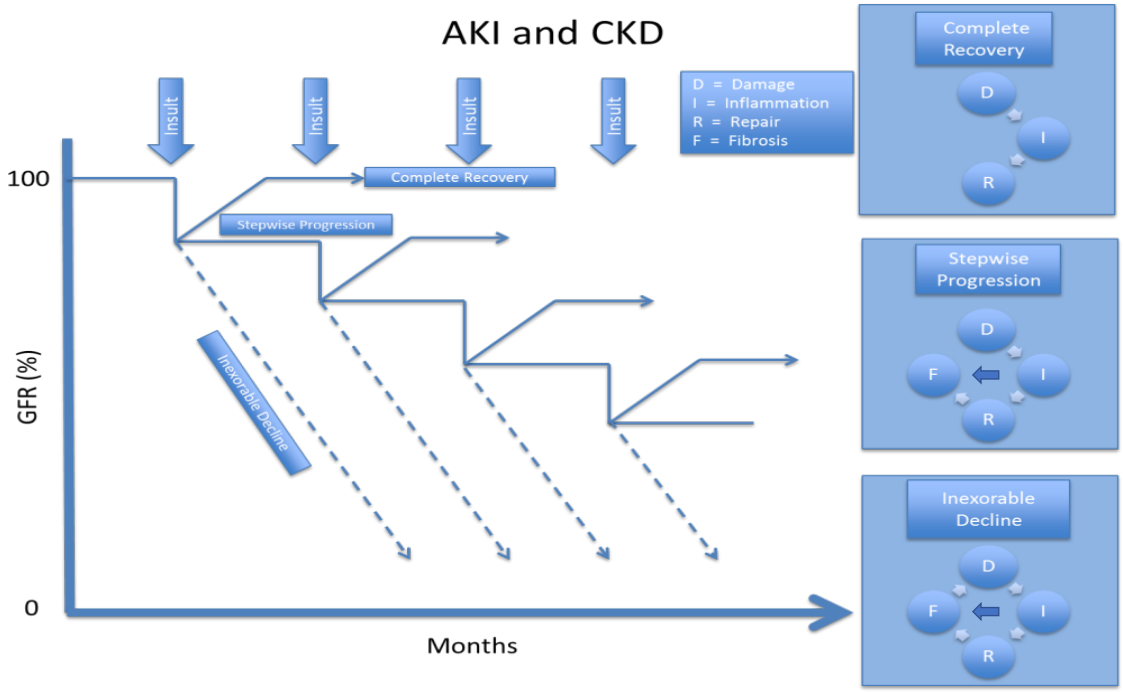


Figure 1c: AKI and CKD

Figure 1: Conceptual Model of GFR and cellular pathology over time in AKI, CKD and AKI and CKD

1a: The cellular phases of AKI leading to repair, highlighting the possibility of initiating a self-perpetuating cycle of inflammation producing fibrosis leading to CKD.

1b: The phases of cellular injury in chronic kidney disease. Following an initial insult there is initiation of the inflammatory response with repair. This may then lead to the extension phase with added fibrosis. Past a point of no return the disease process embarks upon a self-perpetuating cycle of cellular damage and fibrosis (maintenance phase) leading to deterioration in GFR, and progression to end-stage renal disease (ESRD). The figure also shows the effect of intervention on the disease process.

1c: The effect of episodes of acute kidney injury on the progression of chronic kidney disease, with 3 possible outcomes; complete recovery, stepwise progression and inexorable decline.

In an ischaemia-reperfusion injury model of AKI in rats Basile et al found permanent alterations in renal structure and function associated with development of features indicative of CKD. [29] They suggest permanent changes in renal blood flow occur following AKI, resulting in tubulointerstitial fibrosis and altered medullary tonicity (causing impairment of urinary concentrating ability). [29] They also suggest a loss of microvasculature resulting in a build-up of extra-cellular matrix, contributing to development of interstitial fibrosis, [29] leading to development of CKD. They hypothesise that as long as there is adequate functional reserve the single-nephron GFR of surviving nephrons increases to

maintain a constant total GFR. [29] This suggests that even in patients in whom creatinine and GFR return to baseline, there may be underlying permanent damage, masked by compensatory mechanisms. These patients may subsequently have an increased risk of CKD and AKI, due to underlying 'subclinical' damage.

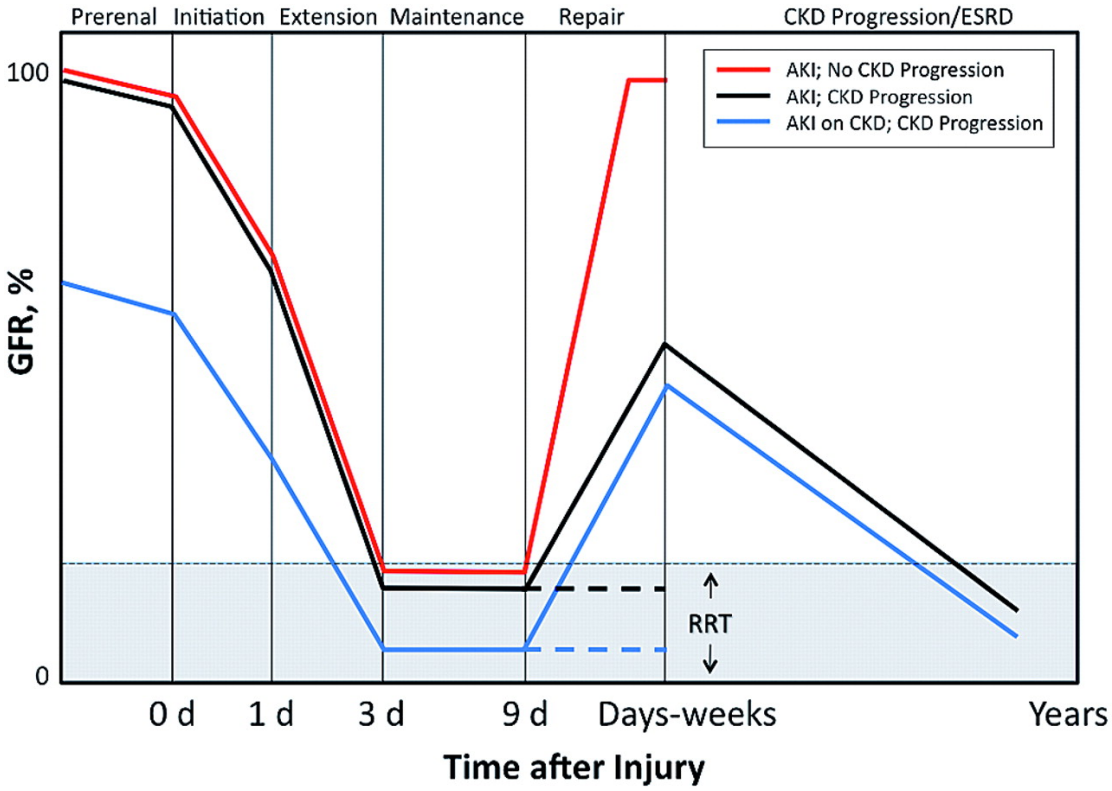


Figure 2: Outcomes and natural history of AKI

Four possible outcomes include (1) full recovery, (2) incomplete recovery resulting in CKD, (3) exacerbation of pre-existing CKD accelerating progression to ESRD, and (4) non-recovery of function leading to ESRD. [28,30]

These results are borne out further by studies of renal transplant patients, which demonstrate that delayed graft function (most commonly acute tubular necrosis (ATN)) [31]), is an independent risk factor for graft survival. [31-33] The kidney has the ability to restore structure and function following AKI, but there are some changes and damage, which are permanent. This may lead to development of CKD (or progression of existing CKD) if there is not sufficient functional reserve to compensate. In cases where compensation maintains baseline GFR, there may then be increased risk of future development of CKD. This 'subclinical' damage will be important in the management of these patients following AKI, to prevent progression or development of CKD.

Does this all suggest that AKI and CKD are biologically part of the same pathway, with eventual glomerulosclerosis and interstitial fibrosis? The discrete episodes of AKI leading to fibrosis by setting up the cycle of inflammation and cell repair.

Incidence

So how many people does acute kidney injury affect? It is estimated that in the United States, 17 million admissions per year are complicated by AKI.[34] Whereas in the developing countries where AKI is a disease of the young[35-37] and children, [38,39] in developed countries it is a disease of the elderly.[40,41] With overall decreases in birth rate and mortality, life expectancy is increasing and is now beyond 80 years in most developed countries. This ageing population, with age-related changes in the kidney, systemic vasculature and immunological system, along with the burden of co-morbidity and exposure to iatrogenic insults such as medications, radio-contrast agents and surgery, will lead to a continued rise in the incidence of AKI. It had been suggested that the incidence will nearly double in the next decade.[40,42] Reported incidences will also rise as with increased understanding in the medical community there will be greater awareness and reporting of its presence and also the recognition of risk which will lead to increased testing.

The incidence of AKI has been reported as 486-630 pmp/year in data from the last 10 years.[43-45] In 2003 Ali *et al* from a population of 523,390 in the Grampian region of Scotland, conducted a population based study of AKI, reporting an incidence of 1811 cases of AKI and 336 of acute-on-chronic renal failure (ACRF) per million population. [46] This study reported a much higher incidence than previous work and may be closer to the true incidence of AKI.

The varying incidences reported in the literature are most likely to be related to differing definitions used historically to define AKI. This will be discussed further in this chapter and also in Chapter 2 ('Define the Epidemiology of AKI'). With increased recognition of AKI over the last decade, and the low cost of renal

function testing it is also likely that there has been an increase in testing, resulting in increased detection and reporting.

Outcomes

So what are the outcomes for the patient with AKI? There is clear evidence that outcome from AKI is poor. From historic local data, only 56% of patients who experienced severe AKI in hospital survived to discharge; only 28% survived to 3 years post discharge. [43] Most studies of AKI in the intensive care unit (ICU) report a mortality exceeding 50%. It is clear that ICU and in-hospital mortality increases with severity of AKI. [1,4,46-56]Despite the trend in recent years for lower mortality, AKI still remains an important negative prognostic factor, particularly in critically ill patients. Even small isolated increases in serum creatinine have an associated increase in short-term morbidity and mortality and in longer-term outcomes including 1 year mortality; [39,49,61,68-72] even more so when renal replacement therapy (RRT) is required. [5,6,13,34,57] A study from the Medicare Sample Beneficiary Analytical File from 1992 to 2001 found that patients with AKI who required RRT had an in hospital mortality of 32.9%, compared to 27.5% in patients with AKI without requiring RRT, and 4.6% in patients without AKI. Importantly they found the mortality rate was 32.6% in patients with AKI coded as a secondary diagnosis, and 15.2% in patients with AKI coded as a primary diagnosis. [40] This suggests, as is known, that isolated AKI without other organ involvement has a better prognosis than AKI in the context of multi-organ failure.

Chronic Kidney Disease (CKD) is an independent predictor of morbidity and mortality. [58,59] Hence we would assume that AKI in CKD has a summative effect on outcome, raising the question of whether outcome of AKI differs with presence of background CKD. Studies actually demonstrate lower in-hospital mortality in patients with AKI on a background of CKD, compared with patients without background CKD. [41,53,60-64] This would seem counterintuitive. One explanation might be that patients with CKD require less of an insult to manifest clinically apparent AKI, and thus severity of the AKI episode is less in these CKD

patients, resulting in better outcomes. Also, patients experiencing 'silent and discrete' AKI, which remains unrecognised and does not lead to admission, will not be captured by epidemiological studies. Only the more seriously ill patients with clinically apparent and recognised AKI will be included, thus leading to bias in mortality statistics. Conversely those with CKD may have more resilience to acute insults secondary to conditioning or priming, and tolerate AKI better. It is also possible that those with CKD receive better/different care than non-CKD counterparts when AKI is identified, thus impacting outcomes. It has also been suggested that results may be confounded by malnutrition (lower serum creatinine values from low muscle mass). [60]

Even small isolated increases in serum creatinine have an associated increase in short-term morbidity and mortality and in longer-term outcomes including 1 year mortality. [1,2,4,47,65-68] 'Silent and discrete' episodes of AKI in the community therefore require further research directed at recognition and early indentification as intervention in this group may have a significant effect on outcomes.

So far, solely mortality as an outcome of AKI has been discussed. Another outcome of paramount interest is renal recovery. From the annual report of the United States Renal Disease Survey 2006, approximately 6% of patients with AKI progressed to end stage renal disease (ESRD) within 2 years, and two thirds of hospitalised patients who had AKI and progressed to ESRD, had background CKD. [69] CKD or co-morbid conditions leading to CKD are risk factors that predict dialysis dependence following AKI. [70,71] Wald *et al* looked at outcomes of chronic dialysis and death in AKI patients requiring in-hospital dialysis who survived free of dialysis for at least 30 days after discharge, from a 10-year cohort of all adult patients in Ontario Canada. Patients with AKI were 3 times more likely to require chronic dialysis compared to those without. [72] Individuals with pre-existing CKD, who had AKI requiring dialysis, had a 2-fold higher risk of chronic dialysis compared to patients with CKD without AKI requiring dialysis. Patients with AKI requiring dialysis without pre-existing CKD had a 15-fold higher risk of chronic dialysis than patients with CKD without AKI. [72]

Other observational and database studies demonstrate AKI on background CKD leads to ESRD at a higher frequency than does AKI alone. [12,40,46] Ishani *et al* assessed a random cohort of 233,803 hospitalised patients based on Medicare claims, aged ≥ 67 years on discharge and without previous ESRD or AKI. [12] Patients with concomitant AKI and CKD were far more likely to develop ESRD, indicating a strong multiplicative effect of the interaction on ESRD development. [12]A population-based study by Ali *et al*, compared patients with acute-on-chronic kidney disease (ACKD) to those with AKI alone. Patients with ACKD were older, with less chance of renal recovery. [46]

Importantly, as already suggested (and to be discussed later in this chapter) these studies all depend on definition of both CKD and AKI, which may not be accurate or comparable. For example, definition of CKD based on diagnostic coding, or pre-operative GFR taken as baseline function. These can introduce bias in AKI and CKD detection. Singh *et al* suggested differences could also reflect greater specificity of administrative codes for AKI among patients without CKD. [73] This underlines the need for consensus on definition of baseline function. This will be discussed in more detail later.

There is mounting evidence that AKI contributes significantly to CKD and CKD progression, leading to ESRD. As discussed in 'underlying biology', Okusa *et al* (pathophysiological concepts from Sutton *et al*), suggest that following AKI, there are four possible outcomes: (1) full recovery, (2) incomplete recovery resulting in CKD, (3) exacerbation of pre-existing CKD accelerating progression to ESRD, and (4) non-recovery of function leading to ESRD, [28,30] (Figure 2). There could also be a fifth outcome in that AKI does not necessarily have to be associated with progressive CKD. AKI may incompletely recover leading to a step down in GFR, which subsequently remains stable.

There is no doubt mortality from AKI is high. In those that survive, there may be decline in function, in some cases leading to ESRD, either at the time of AKI, or in the future. [51,74-77] Even in patients with complete recovery there is still reduced survival and increased incidence of CKD in the years following AKI. [12,78] Patients

experiencing AKI are likely to also have risk factors for CKD. It may be that patients without known background CKD who develop AKI already have unrecognised renal disease and reduced functional reserve, not yet manifest as CKD. As discussed in 'underlying biology', these patients are programmed to develop future CKD, and the AKI episode simply speeds up the development of overt CKD.

Ishani *et al*, based on Medicare claims, reported that of patients with AKI and no background CKD, 72.1% had CKD documented within 2 years of AKI. [12] Triverio *et al* demonstrated, following AKI 50% of patients without background CKD progressed to CKD within 3 years. [79] Hsu *et al* suggested the growth of ESRD incidence (United States) could not be accounted for solely by rise in CKD incidence. Growth in ESRD incidence may partly be attributable to AKI. [80]
There are further studies suggesting development of CKD, and dialysis dependency following AKI. [1,2,7,9,62,81] Amdur *et al* tested the hypothesis that AKI and specifically acute tubular necrosis (ATN), causes CKD. 5,404 of 113,272 patients (United States Department of Veterans Affairs database, 1999 to 2005) had diagnostic codes indicating AKI or ATN without background CKD. [82] A diagnosis of ATN, without background CKD, was associated with time to development of CKD stage 4 comparable to a patient with early CKD. Twenty per cent of survivors of ATN rapidly progressed to CKD stage 4. Diagnostic codes of AKI and ATN were associated with significant decline in function over time after hospital discharge. Survivors of AKI were more likely than controls to progress to late-stage CKD. The authors concluded that AKI, may be an important cause of CKD. [82]

If AKI is a cause of CKD, it seems logical AKI may progress pre-existing CKD. There are however difficulties in testing this hypothesis. A large number of risk factors for AKI are those of CKD. AKI also occurs more frequently in an older population with greater burden of co-morbidity, in which there may be greater risk of CKD progression anyway. Many studies looking at outcome following AKI, concentrate on survival and subsequent ESRD development, however resultant

CKD and CKD progression are less well reported. These studies also again depend on definitions used.

Could minor episodes of AKI in the community, not appreciated to have occurred as renal function is either not tested or not properly assimilated, be contributing to development and/or progression of CKD? The effect of 'silent and discrete' episodes of AKI in the community on CKD progression is presently unknown. There is growing evidence that 'multiple hits' may well contribute to progression in susceptible individuals.

Following an episode of AKI, KDIGO guidelines suggest we should evaluate patients within three months for resolution, and at three months or after for new onset or worsening of pre-existing CKD. They also suggest if patients do not have CKD they should be considered at increased risk, on the assumption that one AKI episode demonstrates 'susceptibility' and qualifies a high-risk population. Further research is warranted to inform the optimal follow up period and better understand the clinical consequences of AKI in patients with and without underlying CKD. [83]

Again, as previously suggested, the above reported studies depend on the definitions used, with varying outcomes likely to be biased dependent on definition of AKI. To this extent it is difficult to appreciate the 'true' outcomes of AKI.

Why is AKI under the spotlight?

The concept of acute kidney injury (AKI) or as it was previously acute renal failure is not new. There was renewed interest in acute renal failure dating from the now classical description of tubular degeneration and tubular pigmented casts, together with intact glomeruli, in patients crushed by fallen masonry during the London blitz. [84] However in the last 5-10 years there has been a growing impetus and focus on AKI both within the academic community and politically within government and the National Health Service (NHS). Within the Department of Health, NHS Kidney Care (the work of NHS Kidney Care has now

come to a close) brought together experts in AKI from across the country to form the AKI Delivery Group. This has led to an AKI National programme, which includes the workstreams: education, risk, detection, measurement, intervention and implementation. There has also been the development and promotion of the 'Think Kidneys' NHS campaign ('Think Kidneys' is the brand name for the UK Renal Registry's Acute Kidney Injury National Programme) to "improve the care of people at risk of, or with, acute kidney injury". They have increased awareness of AKI, and actively promoted better clinical management. There has also been the development of guidelines; the KDIGO (Kidney Disease: Improving Global Outcomes) AKI guideline,[83] the recent NICE (National Institute for Health and Care Excellence) guidance on AKI ('Acute kidney injury: prevention, detection and management', NICE CG 169),[85] and the updated Renal Association Guidelines. [86] AKI has also now been incorporated as a clinical pathway in the Enhancing Quality Initiative.

There has also now been the NHS England Patient Safety Alert for AKI, incorporating the NHS England AKI algorithm to standardise AKI detection and diagnosis across England (see Appendix 9).

So why is AKI, which is not a new entity, now under the spotlight?

Definition

As suggested previously, the first debate in acute kidney injury was and is definition. Over the years one inherent problem in both diagnosing AKI clinically and reviewing and comparing studies published in the literature has been the numerous definitions used to define AKI. [87] Use of these differing definitions in different locations with different populations has only worsened the problem. It also precluded the appreciation of the true problem of AKI in terms of incidence and outcomes, as will be addressed in Chapter 2.

RIFLE

In 2003 the Acute Dialysis Quality Initiative (ADQI) group published guidelines to define AKI as either a 1.5-fold increase in serum creatinine, a decrease in estimated glomerular filtration rate (eGFR) by >25% or a reduction in urine output to <0.5ml/kg/hour over 6 hours.[67] They developed the RIFLE, Risk Injury Failure Loss and End stage renal failure (ESRF) classification to define patients by changes in serum creatinine or urine output criteria. [67] Risk was defined as a 1.5-2.0-fold increase, injury as a 2.0-3.0-fold increase, and failure as a >3.0-fold increase in serum creatinine. [67] Loss was defined as a complete loss of kidney function requiring renal replacement therapy (RRT) for > 4 weeks and ESRF as complete loss of kidney function for >3 months.[67] The full RIFLE criteria to define AKI is documented in Table 1.[88]

Table 1: The RIFLE (Risk, Injury, Failure, Loss, ESRF (End Stage Renal Failure)) criteria to define AKI.[88]

	GFR Criteria	**Urine Output Criteria**
Risk	↑sCR x 1.5 or ↓GFR>25%	UO <0.5ml/kg/h for 6 hours
Injury	↑sCR x 2 or ↓GFR>50%	UO <0.5ml/kg/h for 12 hours
Failure	↑sCR x 3 or ↓GFR>75%	UO <0.5ml/kg/h for 24 hours or anuria for 12 hours
Loss	Complete loss of kidney function for >4 weeks	
ESRF	Complete loss of kidney function for >3 months	

AKIN

In 2007 the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria, defining 3 stages of AKI (Table 2): AKIN 1 equating to the "R" of the RIFLE criteria with the inclusion of a rise in serum creatinine of 1.5-fold or 26.4μmol/l (0.3mg/dl), AKIN 2 as the "I" and AKIN 3 as the "F" of the RIFLE criteria.[89] The "L" and "ESRF" were redefined as outcomes.

The addition of a rise in 26.4μmol/l to define AKIN 1 was based on 2 large studies, which demonstrated an independent association between an increase in serum creatinine of 26.4μmol/l and in-hospital mortality.[34,57] RIFLE and AKIN are consensus definitions which have now been validated and correlate well with patient outcomes. [90,91]

Table 2: The Acute Kidney Injury Network (AKIN) staging of acute kidney injury (AKI) by serum creatinine and urine output criteria. [89]

Stage	**Serum creatinine**	**Urine output**
AKIN 1	≥ 1.5-1.9 times baseline OR 0.3 mg/dL (26.4 μmol/L) increase	< 0.5 mL/kg/hr for 6-12 hrs
AKIN 2	≥ 2.0-2.9 times baseline	< 0.5 ml/kg/hr for ≥ 12 hrs
AKIN 3	≥ 3.0 times baseline OR Increase in creatinine to ≥ 4 mg/dL (354 μmol/L) with at least an increase of 0.5mg/dL (44 μmol/L) OR Renal replacement therapy In patients aged <18yrs decrease of eGFR to less than 35 mL/min/1.73m^2	< 0.3 ml/kg/hr for ≥ 24 hrs OR Anuria for ≥ 12 hrs

KDIGO

In the recent KDIGO AKI guideline (2012), AKI is defined as a syndrome, including direct *injury* to the kidney as well as acute *impairment* of function. [83]
The guideline defines AKI as:

- Increase in serum creatinine by >0.3 mg/dl (26.4 µmol/l) within 48 hours, or
- Increase in serum creatinine by >1.5-fold above baseline which is known or presumed to have occurred within 7 days or
- Urine volume <0.5 ml/kg/h for 6 hours.

The importance of staging AKI (Table 2) is stressed, as adverse outcomes worsen with increasing stage. [46-49,83,92-94].

The definition of both AKI and CKD are both time dependent. For AKI there must be an increase in serum creatinine over a period of 2 (AKIN) to 7 (RIFLE) days. For CKD glomerular filtration rate (GFR) must be reduced for at least 3 months. These definitions may not capture all cases of AKI and CKD. Certain causes of AKI and CKD may lead to changes in serum creatinine and GFR over a time period outside those currently specified, precluding definition. These cases should not be neglected, as intervention may be required. For this reason, the KDIGO AKI Work Group proposed an operational definition for acute kidney diseases and disorders (AKD), to provide an integrated clinical approach to patients with abnormalities of kidney function and structure, and provide a diagnostic algorithm for defining AKD, AKI and CKD (Table 3). [83]

Table 3: The definitions of AKI, CKD, AKD and NKD. [83]

	Functional Criteria	**Structural Criteria**
AKI	Increase in serum creatinine by 50% within 7 days, OR	No criteria

	Increase in serum creatinine by 0.3 mg/dl within 2 days, OR Oliguria	
CKD	GFR <60 for >3 months	Damage for >3 months
AKD	AKI, or GFR <60 for <3 months, OR Decrease in GFR by ≥35% or increase in serum creatinine by >50% for <3 months	Kidney damage for <3 months
NKD	GFR ≥60 Stable serum creatinine	No damage

AKI, acute kidney injury; CKD, chronic kidney disease; AKD, acute kidney diseases and disorders; NKD no known kidney disease; GFR, glomerular filtration rate (ml/min/1.73 m^2). [83]

It is important to note that in the majority of clinical practice and in research using retrospective database analyses as described here, solely the serum creatinine criteria are used to define acute kidney injury (AKI). The changes in urine output are a more sensitive marker of AKI and allow more rapid detection as changes occur much sooner. However, outside of the intensive care setting in the non-catheterised patient the determination of urine output per hour is very difficult.

AKI and AKD often occur in patients with CKD. What previously made the determination of the epidemiology of AKI and CKD, and the interplay between the two, more difficult was the variation in definitions used and populations studied. The 'true' epidemiology of acute kidney injury will be addressed in Chapter 2.

Baseline

Although we now have an internationally agreed and validated definition of AKI, the time constraints of these definitions raise the big question and one focus of the present debate in AKI, in how we define the baseline kidney function for a patient. The absolute and relative rises in serum creatinine to define AKI are now used widely in clinical practice and research studies allowing better comparison of data sets. However what baseline kidney function are these rises, absolute or relative, from? The AKIN criteria, suggests a rise in serum creatinine over a period of 2 days and the RIFLE criteria suggests a rise over a period of 7 days. However, in a large number of patients presenting acutely to hospital, they will not have had blood tests in the preceding 2 or in fact 7 days. The question and debate is then twofold; how far back do we look for a baseline kidney function, and what value over this time period do we take?

A retrospective cohort study by LaFrance and Miller assessed 1,126,636 veterans (US Department of Veterans Affairs healthcare system), who were hospitalised at least once between 2000 and 2005.[95] The highest serum creatinine during hospitalisation was compared with the lowest using 4 different baseline periods (in-hospital only, 3, 6, or 12-months pre-admission). AKI was defined as a rise in serum creatinine ≥1.5 times or an increase of 0.3-0.5 mg/dl over baseline. [95] The cumulative incidence of AKI ranged from 12.5% (in-hospital baseline), to 18.3% (baseline up to 12-months pre-admission). By extending the baseline period to at least 3 months they found the discriminative power increased slightly (C statistic increased from 0.846 to 0.855; p = 0.001). They suggested the need for consensus on how baseline serum creatinine should be determined in database studies.

Previously, when a clinician defined baseline kidney function this was often achieved through the visualization of serum creatinine results graphically represented, and providing a subjective assessment of baseline visually. However, to objectively quantify and standardise the definition strict mathematical parameters, however simplified must be employed. One solution,

as reported by LaFrance and Miller is to define the baseline kidney function as the lowest serum creatinine in the preceding 12 months (allowing a computer algorithm to define AKI from creatinine results in a structured database).

However, the problem with this method is that a spuriously low result recorded on the pathology database, either from an error or more often from for example fluid loading and hence dilution during a previous hospital admission, will be taken as the baseline kidney function (Figure 3a). This could in fact be significantly lower than the patient's true baseline kidney function, leading to an incorrect trigger of a diagnosis of AKI on a new blood test.

There is also the possibility that a patient with progressive CKD may trigger a diagnosis of AKI based on a baseline defined as the lowest serum creatinine in the preceding 12 months, when actually the kidney function has slowly deteriorated over the 12-month period, but comparison of the present creatinine and that of 12-months prior triggers a diagnosis of AKI (Figure 3b). In the same way, within a 12-month period a patient may have a stepwise reduction in kidney function (likely due to an AKI) and hence increase in creatinine that then remains stable. However, a new serum creatinine test, although at the same level as the previous number of months may be higher than the previously lower baseline in the last 12 months, again triggering AKI (Figure 3c).

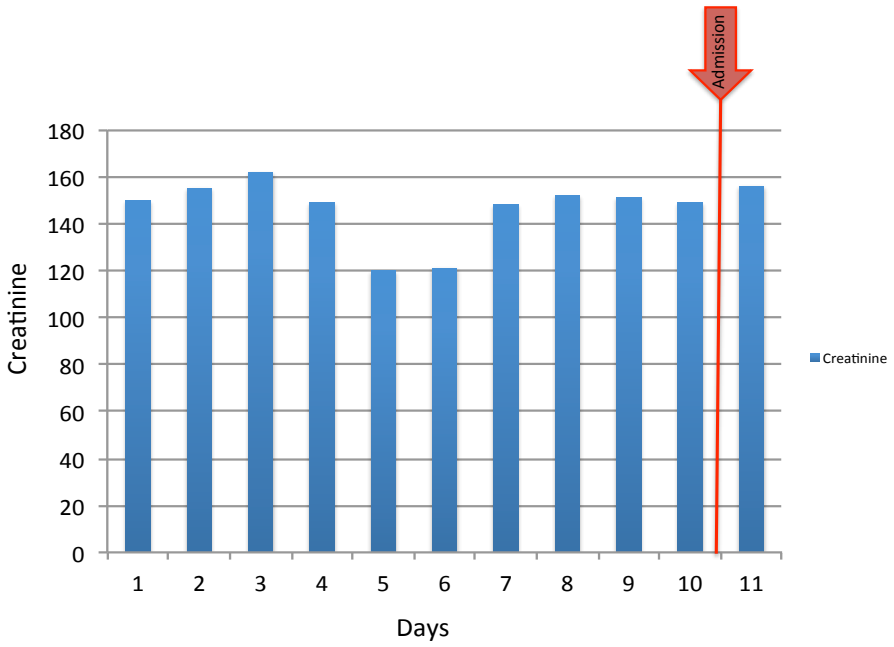


Figure 3a

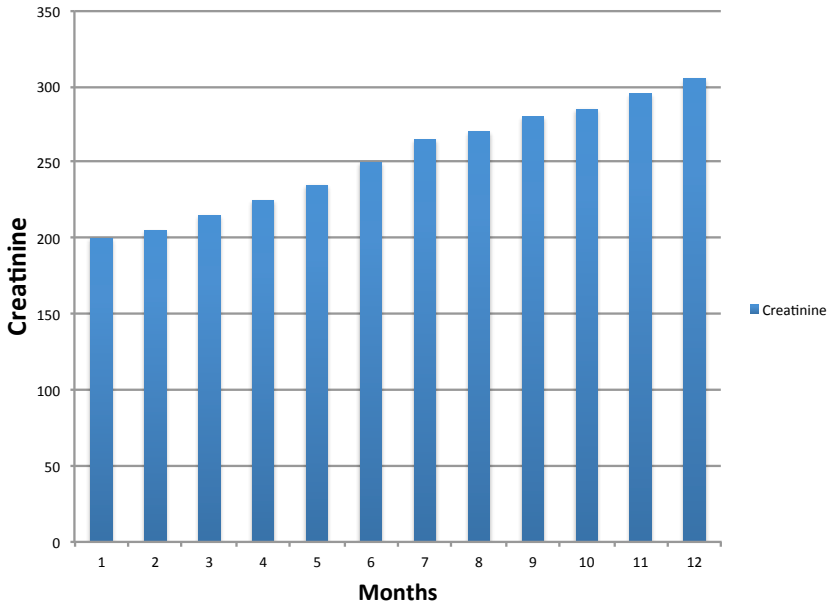


Figure 3b

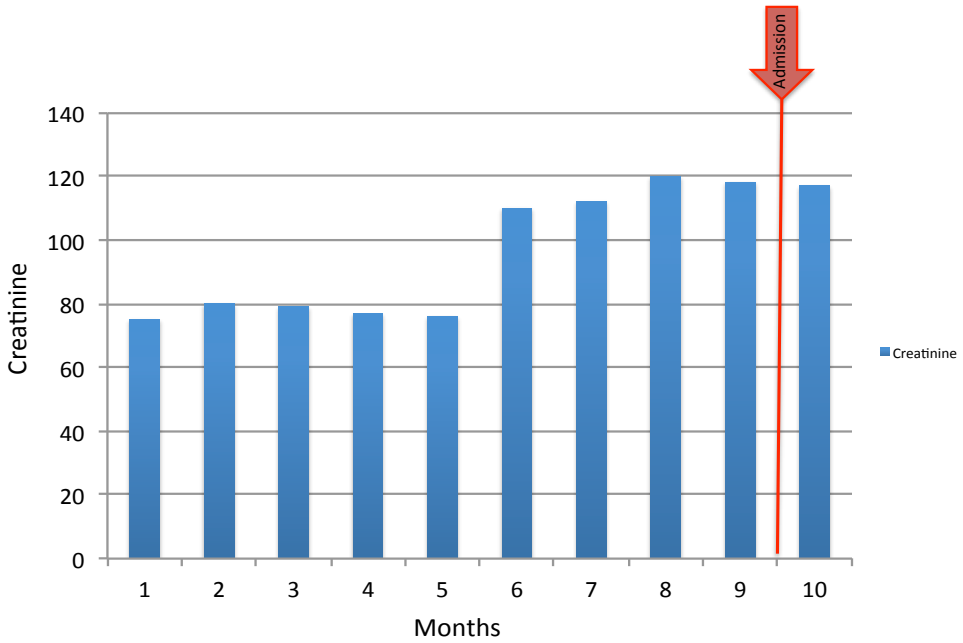


Figure 3c

Figure 3: errors in defining acute kidney injury as the lowest creatinine in the 12 months prior to the present test

a) Here the kidney function (creatinine) can be seen to be stable, however 2 spuriously low results, which may be a result of error or more likely fluid loading and dilution may result in an incorrect definition of AKI.
b) A progressive decline in CKD over the course of 12 months. Using the lowest creatinine in 12 months as the baseline will trigger a definition of AKI.
c) Here there has been a stepwise deterioration in kidney function around 4 months previously (likely to have been an AKI at that point in time), and since then the kidney function has been stable. However, using a 12-month baseline will continue define this as an acute event.

In an attempt to tackle some of these issues, other strategies have been suggested including taking the average of values between 7-365 days prior to admission,[96] back calculating reference serum creatinine (SCr) for missing values from an assumed MDRD (Modification of Diet in Renal Disease) defined glomerular filtration rate of 75 ml/min/1.73m^2 [97] and (more recently) a method employing multiple imputation using known comorbidity strengthened by factoring in the lowest admission SCr.[98]

If there are no previous serum creatinine results in the preceding 12 months, the KDIGO AKI guideline suggests an estimated creatinine can be used, provided there is no evidence of CKD.[83] However there remain cases of CKD in the community that have not been previously appreciated, and hence estimating baseline creatinine may lead to diagnosis of AKI in patients with previously un-recognised CKD. These problems with definition make assessment of AKI and CKD, and their complex interplay more problematic.

One other point to note is the fact that serum creatinine is a poor biomarker of kidney injury, requiring 48 hours for levels to rise following insult. This stresses the need for new biomarkers and point of care devices to allow early identification of patients, aiding early intervention, and indeed more accurate risk assessment to identify patients who may go on to develop acute kidney injury, (see Chapter 5).

While the debate of baseline kidney function in the definition of AKI continues, the now accepted staging of AKI leads to the question of, using these accepted definitions, what the true impacts of AKI are?

To address the issue of variance of definition of AKI across England, and to allow standardisation of definition, NHS England released a patient safety alert, stage three directive on the 9th June 2014, to both ensure all NHS Trusts in England are alerting to AKI (by 9th March 2015) and that there is standardization in the identification of AKI using a single algorithm[99] (Figure 4). This will also allow (through the Renal Registry) collection of standardised epidemiological data on the incidence and outcomes of AKI from across England. The studies reported here (epidemiology in Chapter 2 and risk modelling in Chapter 5) do not use the NHS England algorithm, as these studies were designed and the analysis completed before the publication of this directive. Chapter 5 does however include validation of the risk models using the NHS England algorithm in order to ensure standardisation and future generalizability within the NHS in England.

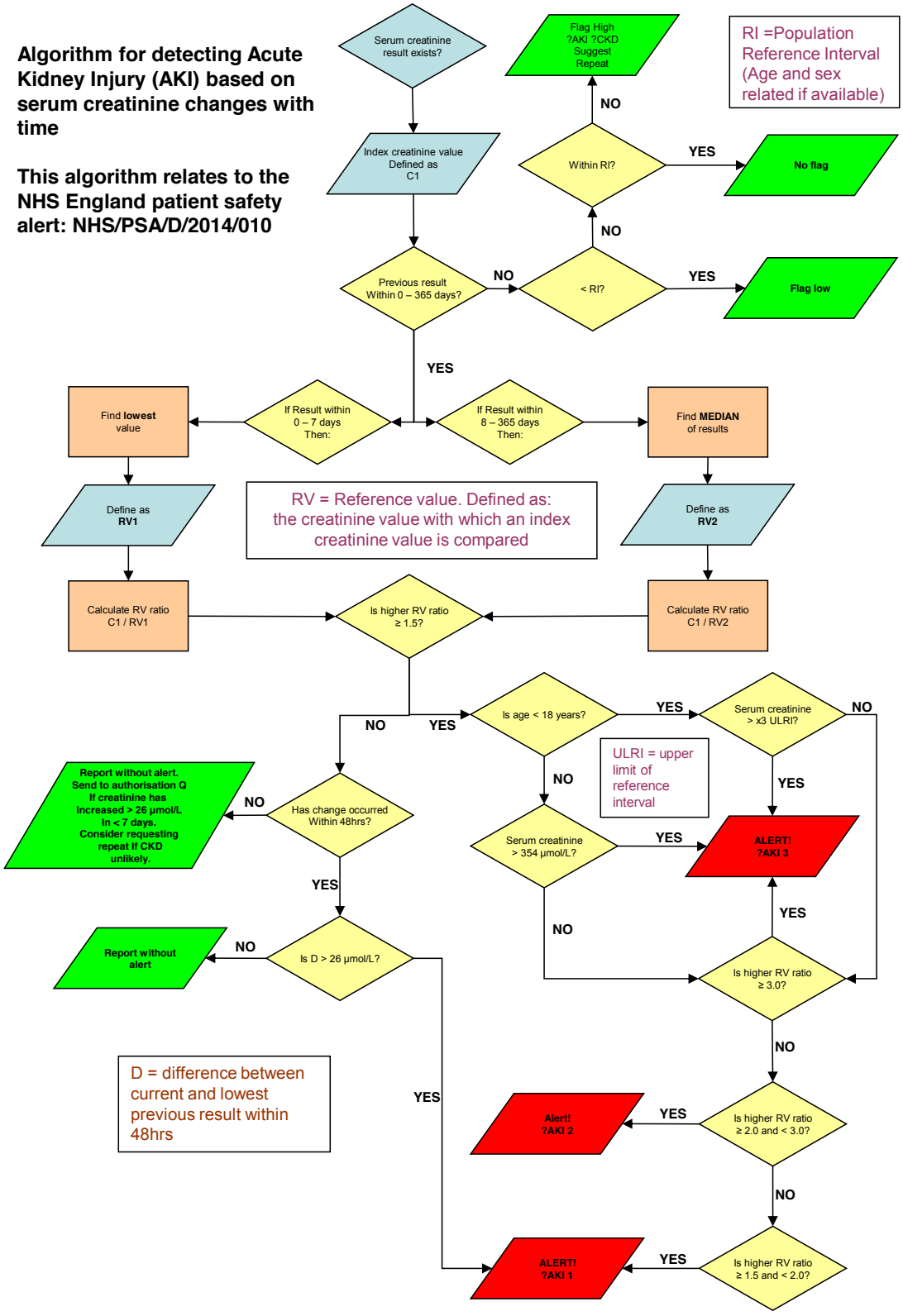


Figure 4: NHS England algorithm for detecting acute kidney injury (AKI) based on serum creatinine changes with time. [99]

NCEPOD

From what we already know about acute kidney injury, it is apparent that early recognition and effective management of AKI is essential, a concept highlighted in the Renal National Service Framework. However, the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the setting of AKI, highlighted systematic failings in identification and subsequent management. [100]

The aim of the NCEPOD study was to assess the care of patients who died in hospital with acute kidney injury, to highlight deficiencies in care and provide recommendations to improve clinical management in the future. An advisory group consisting of nephrologists, anaesthetists, intensivists, and general physicians were brought together to review the care of these patients, with a focus on seven main themes:

- Diagnosis and recognition of AKI
- Recognition of risk factors associated with AKI
- Prevention of AKI
- Assessment of patients recognised as being in AKI
- Management of established AKI
- Recognition and management of complications of AKI
- Organisational factors relevant to the treatment of AKI

All NHS hospitals in England, Wales and Northern Ireland were expected to participate. Hospitals in the independent sector and public hospitals in the Isle of Man, Guernsey and Jersey, also participated. The inclusion criteria was set as any patient 16 years or older who died in hospital between January 1st 2007 and March 31st 2007 inclusive, and who had a coded diagnosis of acute kidney injury. Patients were excluded if they were already receiving renal replacement therapy, or their admission was for palliative care from the outset. At each hospital the NCEPOD Local Reporter, who acted as a liaison between NCEPOD and the hospital staff, facilitated the identification of these cases within the

inclusion criteria, and then facilitated dissemination of questionnaires and data collation for these patients. For each patient identified there was a clinical questionnaire sent to the clinician responsible for the patient's care at the time of death, and an organizational questionnaire for each hospital. Photocopies of the patient's case notes were also made and sent to NCEPOD. The case notes and questionnaires were anonymised before the advisor group reviewed each case. [100]

1518 patients from 215 hospitals met the inclusion criteria. Of these, 473 were subsequently excluded for either not being indicative of AKI, or because the admission, at the outset, was for palliative care. In a further 69 cases the case notes were reported as being lost or the consultant in charge of the patient at the time of their death had left the Trust. This left 976 patients. A clinical questionnaire and/or case notes were received for 700 patients (72%). Of the 700 patients, half of the patients were from the specialities of general medicine and elderly care medicine. [100]

In 14% of patients it was the clinician's opinion that the AKI was avoidable. In an overall assessment of care, only 50% of patients were assessed to have received a "good" standard of care, and importantly in the majority of cases in which the care was considered less than good, they were judged to have room for improvement in their clinical care, rather than at an organizational level. This suggests inadequacies in the clinician's recognition of AKI, and of its subsequent management. In the assessment of complications of AKI, in 13% of patients these were missed, and importantly in 17% the advisors assessed that the complications of AKI were avoidable. In 22% the complications were managed badly. In relation to the assessment and management of AKI, the advisors assessed that in only 67% of patients there was an adequacy of investigation of AKI. The advisors also assessed that in 1 in 6 cases there was a failure to recognize the severity of the illness. In patients developing AKI post admission, a fifth were deemed predictable and avoidable, and in 43% judged to have an unacceptable delay in recognizing AKI. [100]

While the NCEPOD report does have its limitations, notably the dependency on clinical coding and its inherent inaccuracies to define AKI, and a patient population in which the outcome in each case was death, the conclusions are very clear; there are currently significant deficiencies in the recognition and clinical management of patients with acute kidney injury. The NCEPOD report recommends risk assessment for AKI in all emergency admissions to hospital, and suggests that predictable and avoidable AKI should never occur. [100]

The NCEPOD report with its clear conclusions has been key to the growing impetus and focus on AKI, and to why AKI is now under the spotlight. This then leads to the question of how we can improve the clinical management of AKI, and how strategies can be put in place to alert to the presence of acute kidney injury (AKI) to allow early intervention to improve clinical outcomes. Like with any disease process however, our ultimate aim should be prevention, and we must develop and assess strategies to define patients at risk of developing AKI to allow early intervention in these patients to minimise their risk and ultimately prevent AKI.

Research questions raised?

From this introduction it is clear that firstly the real problem and impact of acute kidney injury (AKI) on both the patient and the health care economy must be defined. From the defined outcomes of AKI work should then move backwards in the disease process to first alert to the presence of AKI, and ultimately then a further step back in the disease process to define the risk of AKI in order to prevent its occurrence in the first place, (Figure 5).

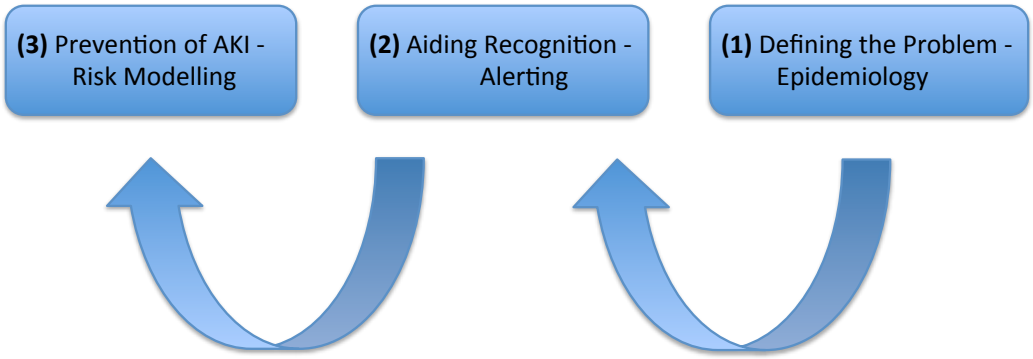


Figure 5: The points of focus / intervention in the studies described here

(1) describing the 'true' problem / epidemiology of AKI, (2) aiding recognition of AKI with the development of alerting methods, (3) aiming to prevent AKI with the development of risk models to alert to patients at risk of AKI.

(a) What is the true epidemiology of AKI?

As the political recognition of AKI gathers pace it is important now with the accepted and validated definitions of AKI to investigate the true impact and extent of this disease. Previous work has employed varying definitions and often in the setting of a large teaching hospital, not providing sufficient insight into the incidence and outcomes of AKI in a typical general hospital setting.
In order to provide a greater understanding of the impact and importance of AKI to the clinician at the point of care, we must have a greater understanding of the "grass roots" epidemiology of AKI. This then provides a clinical context and definition of the problem to be addressed.

(b) How can we intervene early in AKI?

Following on from the NCEPOD report and the clear evidence that effective clinical management of AKI is not occurring, raises the question and debate as to how we can improve this management.

In the disease process of AKI a patient experiences an event. This event may be an illness for example a chest infection, urinary tract infection, or myocardial

infarction, which carry a risk of AKI. This event could also be an iatrogenic risk, for example a radiological scan involving the infusion of intravenous contrast, which again carries the risk of AKI. Once there has been a harm to the kidneys and the patient has a defined AKI there is then the risk of resultant sequelae, for example hyperkalaemia, fluid overload, the need for renal replacement therapy, and the resultant morbidity and mortality.

In this disease process there are therefore 2 points (Figure 6) at which we can intervene in order to improve clinical management and reduce morbidity and mortality. When the patient experiences an event which carries a risk of AKI we can intervene in order to prevent the development of AKI, and when the patient already has AKI we can intervene early in order to reduce the resultant sequelae of AKI and reduce the morbidity and mortality of this disease.

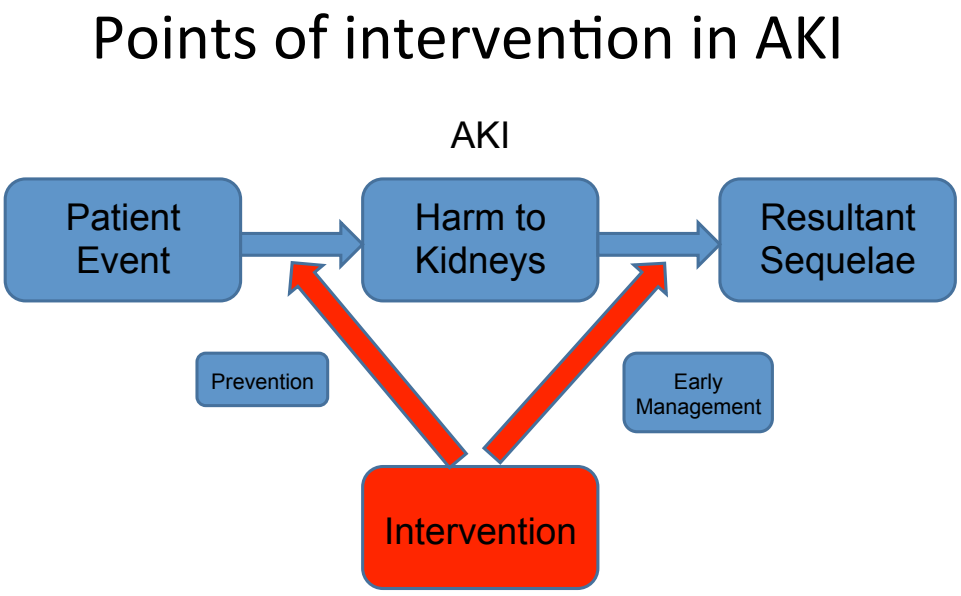


Figure 6: Points of clinical intervention in the disease process of acute kidney injury:

- 'Patient Event' – for example a presenting illness (such as chest infection, urinary tract infection, myocardial infarction) or iatrogenic risk such as contrast media for radiological imaging.
- 'Harm to Kidneys' – the development of overt AKI as defined by creatinine testing described above.
- 'Resultant Sequelae' – such as hyperkalaemia, fluid overload, the need for RRT, all impacting on patient morbidity and mortality, and healthcare resources.

The first stage in improving the management of acute kidney injury is to alert clinicians to its presence as soon as possible. This early recognition will allow optimum management and effective intervention to be instigated early in the disease process in order to improve outcomes in terms of morbidity and mortality. This aids the "early management" documented in Figure 6.

(c) Can we predict AKI?

Although by providing effective alerting to the presence of patients with AKI and intervening at this stage should improve outcomes in AKI, the next step in improving the overall management of AKI would be to intervene one step earlier in the disease process; to prevent AKI in the first place. This is particularly important, as the creatinine from which AKI is defined takes up to 48 hours to rise in the event of AKI. Hence a patient may have suffered an injury to their kidney function, which is not yet evident from their blood creatinine level from which AKI is defined.

To direct specialist and critical care in the management of AKI, it would also be important to define patients who are likely to experience worsening of their AKI. If each patient's risk of AKI, or of worsening AKI if already present, can be defined, then clinicians can be alerted to these patients and management changes and interventions can be put in place in order to prevent or at least reduce the risk of the patient developing AKI, or of experiencing worsening AKI if AKI is already present.

These research questions will form the basis of this thesis.

Chapter 2: Define the epidemiology of AKI

(The work in this chapter is published in a peer-reviewed publication. See Appendix 2: Paper 2: What is the real impact of acute kidney injury?)

A number of studies have documented the incidence of acute kidney injury (AKI) in a variety of populations [34-41,43-46] often in a teaching hospital or solely intensive care setting, but to date the real incidence of AKI in a district general hospital setting has not been accurately documented. Before developing strategies to improve clinical management, first the problem must be defined.

Aims

The aims of this study are therefore to (i) use the acute kidney injury network (AKIN) definition to describe the real incidence of AKI in a typical general hospital setting in an unselected patient population, (ii) describe the associated short and long-term outcomes, (iii) describe the health and social care consequences of AKI.

Methods

Patient Population

Ethical approval for this study was obtained from Kent Research Ethics Committee (ref 10/H1101/89). All adult patients (18 years or over) admitted to East Kent Hospitals University NHS Foundation Trust (EKHUFT) between 1st February and 31st July 2009 were included. Time of entry to the cohort was the date of admission for each patient. EKHUFT comprises 3 general hospitals with a total of 1250 inpatients beds serving a defined population of approximately 744,400 people (582,300 adults) in the geographical area of East Kent in the southeast peninsula of England. Geographically it is assumed that all patients within the area of East Kent present to the 3 hospitals of EKHUFT and hence all

incident cases of acute kidney injury within secondary care in East Kent will be captured by EKHUFT data sources used here. Patients were followed up until the 31st March 2011. Patients receiving chronic renal replacement therapy (RRT) (including dialysis and renal transplantation), maternity admissions and day case admissions were excluded from the analyses.

Data Extraction

Data were extracted from the EKHUFT data warehouse. This data warehouse stores patient demographics and details of all patient episodes, including primary diagnosis and co-morbidity for each episode. Unique patient identifiers were used to link the data warehouse with the pathology database, to provide creatinine blood test results during the inpatient stay, and for the prior 12-month period in order to define baseline kidney function. Renal replacement therapy (RRT) data were extracted from the renal data system (Renal Plus, CHI) and intensive care databases.

Further documentation on data extraction is provided in Chapter 5. The data linking in this study however differs from that in Chapter 5 (where the basic NHS number was utilised to link datasets) as prior to mid 2009 there were significant numbers of records within the pathology database that lacked an NHS number. In order to reduce the "false negative" match rate, where patient blood test results fail to match an inpatient episode because of a missing NHS number, a simple hash was calculated for each pathology result lacking an NHS number to match against an inpatient episode. It is up to twenty-one characters long, and generated in the form:

LLLLLLFFFFFFSDDDDDDDD

With 'L' representing up to the first six non-whitespace characters of a subject's last name, 'F' their first, 'S' their sex and 'D' their date of birth in an ISO-8601 format. Sylvester J. Pussycat, Sr

(https://comicbookrealm.com/report/character/3014/sylvester), born on 1st June 1945 would hash to:

PUSSYCSYLVESM19450601

A hash of this kind does not provide sufficient guarantees against false collisions to be used to automatically match records used for patient care, but limited testing found no false positive results. The collisions produced where, for example, longer names are misspelled after six characters, and the lack of reliance on an assigned number, such as the NHS number, allowed for a high match rate. It is a compact and easily indexed representation, allowing for efficient cross-referencing within the SQL database.

There was no intent to anonymize data by the use of this function, where a one-way hash function such as SHA-256 would be more appropriate.

AKI Definition

AKI was defined by the AKIN criteria using the lowest serum creatinine (SCr) in the 12 months prior to the date of hospital admission as the reference after the method of LaFrance et al.[95] In cases where there were no pre-hospitalisation values and the follow-up SCr (lowest in the 12 months following discharge) was lower than the peak in the study admission, the follow-up creatinine was used as the reference SCr. The assumption was made that if SCr had improved following admission by greater than 26.4 μmol/L, then the admission must have involved an AKI (UK Renal Association, Acute Kidney Injury Clinical Practice Guideline).[86] The peak creatinine during the inpatient stay was used to define the stage of AKI. Of note the analysis here used serum creatinine criteria to define acute kidney injury. As described in Chapter 1 the urine output criteria are more sensitive in detection, however this data is not available in a retrospective database analysis.

All blood testing in East Kent, both from primary and secondary care is stored in a single pathology database, allowing access to blood testing prior to hospital admission to define baseline kidney function.

Independent Variables

Patient demographics (to determine age and eGFR calculations), postcode (to determine deprivation score), co-morbidity (secondary diagnoses), and primary diagnosis were extracted. Both co-morbidity and primary diagnosis were coded for each hospital episode on the data warehouse using ICD-10 (International Classification of Diseases – 10th Edition) codes. For primary diagnoses the ICD-10 group was extracted for each admission. For co-morbidity (secondary diagnoses), validated coding algorithms from Quan et al,[101] with further validated algorithms for diabetes [102] and hypertension, were used to determine a modified Charlson co-morbidity score for each patient. The number of admissions and outpatient appointments in the 12 months prior to a patient admission were also recorded. From the baseline pathology data (creatinine results), the baseline chronic kidney disease (CKD) stage was defined for each patient.

Outcomes

Mortality, hospital length of stay (LOS), intensive therapy unit (ITU) LOS, and change in residence resulting from admission were recorded. Date of death and 30-day re-admission rates were also recorded wherever relevant. The date of death was obtained from the Patient Master Index (PMI) on the hospital patient administration system (PAS). Where a patient died in hospital this field was populated using the discharge details of the patient's episode and was therefore validated at the point the patient was discharged as 'died in hospital'. Where a patient died following discharge the PAS PMI record was updated via a weekly report from the Open Exeter national system, which provides the date of death for any patient recently deceased.[103] Data on LOS, intensive care LOS, re-

admission, and place of discharge were complete, as recorded on the hospital PAS.

All admissions during the recruitment (1st February 2009 to 31st July 2009) and follow-up (1st August 2009 to 31st March 2011) periods were extracted. AKI stage was calculated for all admissions until the end of the follow up in order to inform the survival analysis (as below).
Data were also extracted from the renal data system (Renal Plus, CHI) and from the intensive care database to determine whether patients in this cohort received renal replacement therapy (RRT) during admission, and whether they were still dependent on RRT 90 days post discharge (defined as chronic RRT). Patients who received RRT (often in ITU) but did not meet the creatinine criteria for AKI stage 3, were upgraded to AKI stage 3 in line with the specifications of the AKIN criteria.

Statistical Methods

Patient level demographic summaries were performed, considering a single observation per patient. For patients with more than one admission with AKI during the recruitment period, data were summarised at the time of the admission with their highest stage of AKI where there was a valid reference serum creatinine (SCr). For patients who had no valid AKI recordings over the course of the study recruitment period, data from the first admission was used in the analysis.

Normally distributed data were summarised as the mean and standard deviation. Normally distributed data is symmetrical about the mean. Continuous data not normally distributed were summarised by median and inter-quartile range, or the percentage of values in each category for categorical variables. Three of the continuous variables, modified Charlson co-morbidity score, number of admissions in the previous 12 months, and number of outpatient appointments in the previous 12 months all had a very highly skewed distribution. Skewed data is that in which there is not a symmetry in the

probability distribution about the mean. Variables with these distributions must be treated differently to ensure that outlying values are not overly influential.
So that outlying values were not overly influential, these three variables were categorised for analysis.

Chosen outcomes of interest were mortality, length of stay (LOS), intensive therapy unit (ITU) utilisation, and increase in care following discharge. Regression analyses were performed to determine the impact of AKI on each outcome. Regression analysis is a technique to determine relationships between variables and importantly between predictor variables and the outcome variable of interest. Variables used in the regression model, and thought to be confounders were: age, gender, primary diagnosis, modified Charlson co-morbidity score, stage of chronic kidney disease (CKD), admission from residential or nursing care, deprivation index, and hospital admissions and outpatient appointments in the last 12 months. The analyses were performed in three stages. In the first analysis, the effect of AKI upon each outcome was examined (an unadjusted analysis). The second analysis was age and gender adjusted and the final analysis was multiply adjusted for the above variables.

For primary diagnosis in the regression model, specifically for elective admissions there were diagnosis groups with too few events, which would have led to small sample bias. Therefore, elective admissions were set as the reference and emergency admissions split by ICD-10 group for primary diagnosis, under the assumption that a patient being admitted electively for a procedure or investigation, should not be unwell and present with an event precipitating AKI. However, this assumption may not be valid in the case of elective major operations for example abdominal or vascular surgery, which although the patient presents to hospital clinically well, has a significant risk of developing AKI during their hospital stay as a result of the operative procedure or resultant post-operative complications (for example chest infection, hospital acquired pneumonia).

Logistic regression was used for the analysis of in-hospital mortality and Cox regression for survival analysis.

Logistic or logit regression is the development of a regression model where the outcome (dependent) variable is categorical. The outcome of interest in this case is in-hospital mortality which is a binary dependent variable with the potential binary outcome of either 'died' or 'did not die' in hospital, and as such binary logistic regression is utilised here. Logistic regression utilises a logistic function (the cumulative logistic distribution) to estimate probabilities and determine the relationship between and the effect of the independent variables (in this case the predictors such as age, co-morbidity, gender etc.) on the dependent outcome variable which is this case is in-hospital mortality.

Cox regression is a proportional hazards model used in survival analyses which relates the time until an event occurs (in this case death) with predictor variables which are associated with this time. Hence the length of time until the outcome (death) occurs is related to the predictor variables (for example age, gender, co-morbidity). Cox regression estimates the effects of these variables on the time to the event. The regression model has two constituent parts, firstly the baseline hazard function which describes how (at baseline of the predictor variables) the risk of the outcome (death) occurring changes over time, and secondly the effect parameters which describes how this risk changes with respect to changes in the predictor variables (for example age, gender, co-morbidity).

A time dependent risk analysis for survival was employed to allow adjustment for multiple admissions during the study and follow up period. It was recognised that over the period of follow-up following an index admission with acute kidney injury, the patient may experience further admissions, which could also involve acute kidney injury. These further admissions could significantly impact on a patient's survival during follow-up irrespective of the index definition of AKI. For example, if a patient experienced AKI stage 1 during the recruitment period, however subsequently during the follow-up period they experienced an

admission with AKI stage 3, it is more likely that the AKI stage 3 will have defined their survival in follow-up than the AKI stage 1. Therefore, the time dependent risk analysis involved the elevation of risk at the point of experiencing a higher stage of AKI during the follow-up.

Analysis of length of stay (LOS), which was highly skewed, was performed using negative binomial regression. Skewed data is that in which there is not a symmetry in the probability distribution about the mean. Variables with these distributions must be treated differently to ensure that outlying values are not overly influential. In the case of length of stay (LOS) the majority of patients have a low length of stay of 0-4 days, however there are then outliers with lengths of stay significantly higher for example 50-100 days. This is a positively skewed distribution of values for length of stay. These skewed datasets must be treated differently in terms of regression methods. In a skewed dataset the mean and variance are not the same and therefore we cannot use regression methods that assume a Poisson distribution as we will get a poor fit of the model produced. In this case we can use negative binomial regression which utilises a negative binomial distribution in which the variance and mean are not equal. In this distribution the variance is a function of the mean with the inclusion of a dispersion parameter. With increase in the dispersion parameter there is convergence of the variance to the same value as the mean.

The analysis of LOS was performed at the admission level in the recruitment period, and hence patients may have contributed to the analysis several times during the recruitment period by having a number of admissions during this time. Admissions from a single patient are more likely to be similar than admissions from different patients. To allow for the correlation between repeat LOS values from the same patients (grouped or clustered data) a multilevel approach was employed, equivalent to fitting a random-effects model for subjects in addition to the fixed effects model. The model can vary to two levels both within each patient, and between patients.

In order to assess the social impact of AKI the change in residence related to the admission was assessed. An increase in care from home prior to admission to hospital, to residential or nursing care on discharge, was classified as an increase in care on discharge. This assessment was performed by stage of AKI.

Results

Population Characteristics and AKI

During the 6-month recruitment period there were 66,829 admissions in 45,621 adult patients (Figure 7).

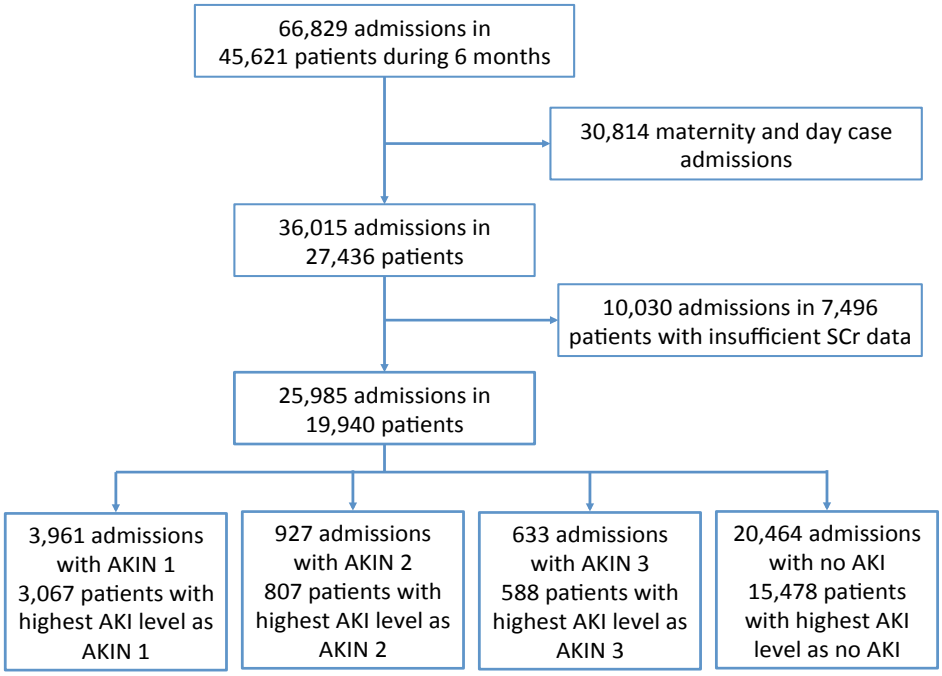


Figure 7: Derivation of the study population.

A diagrammatic representation of the derivation of the study population, at each stage split into the number of distinct admissions, and also the number of individual patients. 30,814 admissions were excluded as they were maternity or daycase admissions, and 10,030 admissions in 7,496 patients were excluded as there was insufficient creatinine data available to allow the definition of acute kidney injury.

After exclusion of maternity and day-case admissions there were 36,015 admissions in 27,436 patients (79.1% of patients had 1 admission during the 6-

month recruitment, 14.6% had 2 admissions, 4.1% had 3 and 2.2% had 4 or more). Overall, there were 10,030 admissions in 7,496 patients with insufficient SCr data to define AKI. Of these 42.9% were elective admissions and 57.1% were non-elective, the majority had a LOS of 0-2 days (see below). Of the 25,985 admissions in 19,940 patients with sufficient SCr data, there were 20,464 admissions with no AKI and 5,521 admissions (15.3% of non-maternity and non-day-case admissions) with AKI. Of these, 3,961 admissions had AKI stage 1, 927 admissions AKI stage 2, and 633 admissions AKI stage 3. Of the 5,521 admissions with AKI, 4064 had AKI on admission (73.6%) and 531 of 633 admissions with AKI stage 3 (83.9%) had AKI on admission.

Of the 36,015 admissions, baseline creatinine data in the 12 months prior to admission was available in 31,435 (87%). In the remaining 4,580 admissions the lowest creatinine in the 12 months following discharge (in survivors) was used as the baseline serum creatinine. In these 4,580 admissions, 7.2% had AKI stage 1, 1.4% AKI stage 2 and 1.3% AKI stage 3. This is in comparison to admissions in which a baseline from the 12 months following discharge was not used, in which 11.5% had AKI stage 1, 2.7% AKI stage 2 and 1.8% AKI stage 3. In admissions culminating in mortality baseline creatinine data was obtainable in 1209/1379 (88%). Overall, only 455/5,521 admissions with AKI (8.2%) involved the calculation of a baseline using the lowest creatinine in the 12 months following discharge.

For descriptive statistics patients without sufficient SCr data ("no AKI info") are reported in the results but only those patients with valid SCr data sufficient to define AKI were included in the regression analyses. Patients with insufficient data to define AKI were younger, had less co-morbidity and shorter LOS than other patients (Table 4).

Table 4: Population demographics and co-morbidity by stage of acute kidney injury (AKI)

Summaries of mean age, gender, deprivation and co-morbidity at a patient level, only considering admissions during the recruitment period, and for multiple admissions per patient during the recruitment period selecting the patient's admission with the highest AKI stage.

Variable	No AKI (n=15,478)	AKI Stage 1 (n=3,067)	AKI Stage 2 (n=807)	AKI Stage 3 (n=588)	No AKI info (n=7,496)
Age - Mean (SD)	62.0 (20.3)	74.2 (16.3)	76.1 (14.7)	72.5 (15.7)	54.2 (21.0)
Age: 18-39	17.1%	5.1%	3.6%	4.4%	29.0%
40-59	23.7%	11.3%	8.9%	16.0%	28.3%
60-79	36.9%	38.2%	37.3%	40.7%	29.5%
80+	22.3%	45.5%	50.2%	39.0%	13.2%
Male Sex - %	45.1%	52.2%	45.0%	49.8%	45.8%
Deprivation - Median (IQR)	17.4 (11.8 27.0)	17.2 (11.8, 25.8)	17.3 (11.8, 25.8)	17.2 (11.9, 26.9)	17.2 (11.7, 26.7)
AIDS - %	0.1%	0.1%	0.1%	0.0%	0.0%
Malignancy - %	6.2%	11.5%	14.0%	16.7%	4.8%
CHF - %	2.6%	10.4%	13.9%	11.6%	1.0%
CPD - %	12.8%	17.0%	16.1%	17.4%	8.5%
Cerebrovascular disease -%	7.3%	13.5%	12.3%	11.2%	3.4%
Dementia - %	3.2%	6.7%	8.2%	7.0%	1.9%
Diabetes - %	10.3%	20.2%	18.7%	23.8%	6.0%
Hemiplegia. - %	1.3%	1.8%	1.4%	1.5%	0.5%
Hypertension - %	27.2%	39.%	39.3%	39.0%	15.5%
MI - %	3.0%	5.0%	6.0%	3.9%	0.7%
Solid tumour - %	2.0%	3.2%	4.8%	4.4%	0.9%
Liver disease - %	0.9%	1.8%	3.0%	6.1%	0.5%
PVD - %	2.1%	5.4%	6.2%	4.6%	1.0%
Peptic ulcer - %	0.6%	1.2%	1.7%	1.9%	0.4%
Renal disease - %	1.7%	11.2%	16.4%	22.3%	1.1%
Rheumatic disease - %	2.3%	3.9%	3.1%	4.1%	1.1%
CKD - no data	0%	0%	0%	0.7%	34.4%
no CKD	84.8%	61.9%	62.1%	68.2%	58.0%

CKD Stage 3a	10.0%	19.1%	20.1%	15.0%	5.0%
CKD Stage 3b	4.0%	13.1%	12.1%	10.2%	2.0%
CKD Stage 4	1.0%	5.3%	5.5%	2.6%	0.5%
CKD Stage 5	0.2%	0.5%	0.2%	3.4%	0.1%
Charlson ≤0 - %	58.0%	31.9%	25.8%	23.3%	74.5%
1-10 -%	25.9%	29.4%	30.5%	30.1%	17.4%
11+ = %	16.2%	38.8%	43.7%	46.6%	8.2%

Chronic Pulmonary Disease (CPD), Chronic Heart Failure (CHF), Myocardial Infarction (MI), Peripheral Vascular Disease (PVD), Acquired Immunodeficiency Syndrome (AIDS). Note the presence of 'Renal Disease' and stages of Chronic Kidney Disease (CKD). CKD stage here is defined by the Modification of Diet in Renal Disease (MDRD) criteria calculated from the baseline creatinine result . 'Renal Disease' is defined as an ICD-10 coded co-morbidity of renal disease on the hospital data warehouse from the admission.

The crude incidence of AKI in the 6-month period was 3,067 patients with AKI stage 1, 807 AKI stage 2, and 588 AKI stage 3. In total, 4,462 patients from a catchment population of approximately 582,300 adults experienced AKI during the 6-month recruitment period, assuming the same incidence for the remaining 6 months of the year from a population of 582,300 this represents an incidence of 15,325 per million (adult) population per year (pmp/yr).

Co-morbidity as evidenced by the Charlson co-morbidity score was over represented in patients with AKI, and increased with AKI stage (Table 4). Deprivation was not related to AKI stage.

Renal Replacement Therapy (RRT)

Only 77 patients of the 588 patients with AKI stage 3 (13.1%) received renal replacement therapy (RRT). Of these, 16 remained on RRT 90 days (defined as chronic RRT) following discharge (2.7% of AKI stage 3). A further 4 patients who experienced AKI stage 3 in their index admission (admission with highest AKI stage during the recruitment period) who did not require RRT during that admission, subsequently required chronic RRT within 90 days of discharge. There were also 2 patients with AKI stage 1, 2 patients with AKI stage 2 and 1

patient with no AKI info who did not require RRT in the index admission but subsequently required chronic RRT within 90 days of discharge. In total 25 patients were on chronic RRT at 90 days.

Survival Analyses

Throughout follow up survival was related to AKI stage, (Table 5, Figure 8). In the upgraded risk analysis, after 12 months 92% of patients who had no AKI were still alive, in comparison to 28% of patients who experienced AKI stage 3 (Figure 8). Figure 8 demonstrates this graphically in the form of a Kaplan-Meier. Kaplan Meier is used to determine the proportion of patients that survive / live for a certain quantity of time (survival time) following a given occurrence / event. In this case the occurrence / event is an episode of acute kidney injury (AKI). The graphical representation of the Kaplan Meier survival curve allows visual comparison of the survival of different groups of patients, in this case of the categorical variable of AKI, with the groups; 'no AKI', 'AKI stage 1', 'AKI stage 2', 'AKI stage 3'. As time moves forward (across the x-axis) the proportion of patients surviving decreases, and the lower the curve on the graph, the lower the survival in that group of patients.

Table 5: A summary of survival estimates by stage of AKI

A summary of the survival estimates at 6-month intervals along with corresponding confidence intervals.

Variable	No AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3
6m survival (95% CI)	0.94 (0.94, 0.94)	0.77 (0.75, 0.78)	0.48 (0.45, 0.52)	0.39 (0.35, 0.43)
12m survival (95% CI)	0.92 (0.92, 0.93)	0.70 (0.68, 0.71)	0.37 (0.34, 0.40)	0.28 (0.25, 0.31)
18m survival (95% CI)	0.91 (0.91, 0.92)	0.65 (0.63, 0.66)	0.32 (0.29, 0.35)	0.22 (0.19, 0.25)
24m survival (95% CI)	0.90 (0.89, 0.90)	0.59 (0.58, 0.61)	0.27 (0.24, 0.29)	0.18 (0.16, 0.20)

Note the AKI groups are based on 'upgraded' AKI risk. If a patient experiences a subsequent admission during follow-up with a higher stage of AKI, they will be upgraded at that point to the higher stage of AKI.

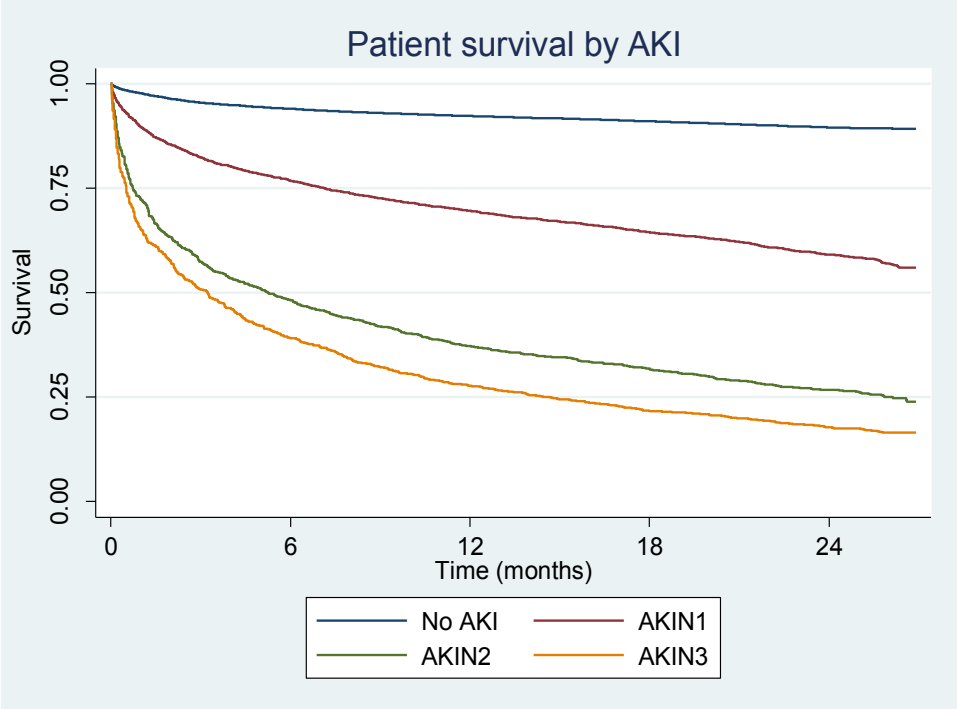


Figure 8: Kaplan-Meier survival by stage of AKI. Note that the AKI groups are based on 'upgraded' AKI risk.

Increasing severity of AKI was associated with increased risk of death and shorter survival even after multiple adjustment, AKI stage 1 almost doubling the risk of death and AKI stage 2 and 3 increasing the risk of death 3.8-fold and 5.5-fold respectively compared to those with no AKI (Table 6).

Table 6: Regression analyses to determine the effect of acute kidney injury (by stage) on outcomes

Regression analyses examining the association between severity of AKI and risk of death, in-hospital mortality, ITU admission, increase in care, hospital re-admission, relative LOS and relative ITU LOS.

		Risk of Death	**In-Hospital Mortality**	**ITU Transfer**	**Increase in Care**	**Hospital Re-admission**	**Relative Length of Stay**	**Relative ITU Length of Stay**
Model	**Stage of AKI**	Hazard Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
1	**No AKI**	1	1	1	1	1	1	1
	AKI	4.85	4.29	2.36	2.71	1.93	1.90	1.38

	Stage 1	(4.51, 5.21)	(3.68, 5.01)	(1.90, 2.93)	(2.17, 3.38)	(1.75, 2.13)	(1.84, 1.97)	(1.13, 1.68)
	AKI Stage 2	12.0 (11.0, 13.1)	16.8 (13.5, 21.1)	4.72 (3.36, 6.61)	3.71 (2.56, 5.38)	2.25 (1.83, 2.76)	2.58 (2.43, 2.75)	1.54 (1.17, 2.01)
	AKI Stage 3	15.6 (14.2, 17.1)	24.7 (18.8, 32.3)	23.8 (16.4, 34.6)	2.27 (1.36, 3.81)	2.09 (1.61, 2.72)	3.07 (3.85, 3.30)	2.25 (1.85, 2.73)
2	**No AKI**	1	1	1	1	1	1	1
	AKI Stage 1	3.11 (2.89, 3.35)	2.98 (2.53, 3.52)	2.63 (2.11, 3.28)	1.61 (1.29, 2.01)	1.69 (1.53, 1.87)	1.68 (1.62, 1.74)	1.43 (1.17, 1.74)
	AKI Stage 2	7.54 (6.89, 8.25)	13.5 (10.5, 17.5)	5.43 (3.88, 7.61)	2.07 (1.43, 2.97)	2.00 (1.63, 2.46)	2.22 (2.09, 2.36)	1.56 (1.20, 2.04)
	AKI Stage 3	11.6 (10.6, 12.7)	25.2 (18.6, 34.5)	23.9 (16.6, 34.4)	1.56 (0.93, 2.60)	1.94 (1.49, 2.53)	2.72 (2.53, 2.92)	2.27 (1.88, 2.76)
3	**No AKI**	1	1	1	1	1	1	1
	AKI Stage 1	1.89 (1.74, 2.04)	2.41 (1.99, 2.91)	2.76 (2.20, 3.46)	1.33 (1.06, 1.67)	1.42 (1.29, 1.57)	1.52 (1.47, 1.58)	1.39 (1.14, 1.69)
	AKI Stage 2	3.81 (3.46, 4.18)	12.1 (8.84, 16.5)	6.03 (4.58, 8.51)	1.49 (1.02, 2.16)	1.50 (1.23, 1.83)	1.88 (1.77, 2.00)	1.42 (1.07, 1.87)
	AKI Stage 3	5.49 (4.97, 6.06)	26.3 (17.8, 38.8)	22.4 (15.5, 32.2)	1.07 (0.64, 1.80)	1.54 (1.20, 1.99)	2.16 (2.01, 3.32)	2.18 (1.77, 2.68)

Intensive therapy unit (ITU) admission: a patient being transferred to and spending any time in ITU during their hospital stay; increase in care: a patient being admitted from home and being discharged to residential or nursing care; hospital re-admission: a patient being re-admitted to hospital within 30 days following discharge; relative length of stay (LOS): the ratio of length of stay in comparison to the length of stay of a

patient without AKI; relative intensive therapy unit (ITU) length of stay (LOS): the ratio of ITU length of stay (in those patients who went to ITU) in comparison to the length of stay in ITU of a patient without AKI.

Model 1. Unadjusted.

Model 2. Adjusted for age and gender.

Model 3. Multiply adjusted for age, gender, primary diagnosis, modified Charlson co-morbidity score, stage of chronic kidney disease (CKD), admission from residential or nursing care, deprivation index, and hospital admissions and outpatient appointments in the last 12 months.

All values are statistically significant, with p values <0.001.

In-Hospital Mortality

Overall, 1,379 (3.8%) of 36,015 hospital admissions in the recruitment period resulted in an in-hospital mortality.

Only 2.0% of patients without AKI died in hospital compared with 8.1%, 25.6% and 33.3% of patients with AKI stage 1, 2 and 3 respectively. AKI severity was significantly associated with in-hospital mortality even after multiple adjustment, the likelihood of mortality increasing 2.4 fold with AKI stage 1 and 12 and 26 fold with AKI stage 2 and 3 respectively compared to patients with no AKI (Table 6).

Length of Stay (LOS)

In those patients who died in hospital LOS prior to death averaged 10.0-13.5 days irrespective of AKI (Table 7). In those surviving to leave hospital LOS was associated with severity of AKI, ranging from a mean LOS of 4.4 days in patients without AKI, to 17.2 days in patients with AKI stage 3. Compared to those with no AKI after multiple adjustment LOS was 1.5, 1.9 and 2.2-fold greater in those with AKI stage 1, AKI stage 2 and AKI stage 3 respectively (Table 6).

Table 7: A summary of the length of stay for: all patients, those who died in hospital, and those who survived to hospital discharge, split by AKI stage.

Statistic	No AKI (n=20,464)	AKI Stage 1 (n=3,961)	AKI Stage 2 (n=927)	AKI Stage 3 (n=633)	No AKI info (n=10,030)
All patients					
Mean (SD)	4.5 (10.5)	9.7 (14.6)	12.3 (16.0)	14.9 (18.5)	2.3 (9.8)

Median (IQR)	2 (0, 5)	5 (1, 12)	7 (3, 15)	9 (4, 20)	1 (0, 2)
0 days	28.6%	12.1%	6.5%	5.1%	37.3%
1 - 2 days	31.2%	22.3%	15.3%	13.0%	46.1%
3 - 5 days	19.0%	18.5%	18.6%	17.2%	9.9%
6 - 10 days	11.2%	19.4%	23.3%	20.2%	2.8%
11 - 20 days	5.8%	14.4%	19.5%	20.9%	1.8%
21 - 50 days	3.4%	11.0%	13.5%	18.6%	1.6%
51+ days	0.8%	2.3%	3.3%	5.1%	0.4%
Hosp mortality					
Mean (SD)	11.1 (14.4)	11.8 (16.3)	10.0 (11.9)	10.3 (12.2)	13.5 (29.1)
Median (IQR)	6 (2, 14)	6 (2, 15)	6 (2, 14)	6 (2, 14)	5 (1, 15)
Survived disch.					
Mean (SD)	4.4 (10.4)	9.5 (14.5)	13.0 (17.1)	17.2 (120.5)	2.1 (8.8)
Median (IQR)	1 (0, 5)	5 (1, 11)	8 (3, 15)	11 (5, 22)	1 (0, 2)

Intensive Therapy Unit (ITU) Utilisation

ITU utilisation increased with increasing AKI severity; 3.9%, 6.8% and 21.6% of patients with AKI stage 1, 2 and 3 respectively were admitted to ITU, compared with 1.8% of patients without AKI. Intensive care LOS also increased with severity of AKI from a mean of 3.0 (SD 7.0) days in patients without AKI, to 4.4 (SD 7.8), 4.5 (5.4) and 7.3 (8.0) days in patients with AKI stage 1, 2 and 3 respectively. After multiple adjustment, AKI severity was again associated with ITU utilisation. Patients were 2.8, 6 and 22 fold more likely to be transferred to ITU with AKI stage 1, 2 and 3 respectively compared to patients without AKI. In patients who went to ITU their length of stay in ITU was 37%, 35%, and 111% longer in patients with AKI stage 1,2 and 3 respectively compared to patients without AKI.

Increase in Care

A greater proportion of patients with AKI (4.5% AKI stage 1, 5.7% AKI stage 2 and 3.7% AKI stage 3) had an increase in care on discharge in comparison to patients without AKI (1.9%). Although having an episode of AKI conferred a

greater risk of increase in level of care post-discharge there was no association with severity of AKI (Table 6).

Hospital Readmission

Having an episode of AKI was also associated with an increase in hospital re-admission within 30 days of discharge compared with those without AKI (Table 6), although again this did not associate with severity of AKI.

Discussion

Summary of main findings

The incidence of AKI in an adult population reported here, 15,325 pmp/yr (10,534 pmp/yr with AKI stage 1, 2,772 pmp/yr with AKI stage 2 and 2,020 pmp/yr with AKI stage 3), is significantly higher than previous estimates reported in the literature,[46] and is likely to be closer to the real incidence in the population. The reasons for the higher incidence reported here are several. This is an unselected in-hospital population; there is increased testing of creatinine due to heightened awareness; the laboratory service in East Kent comprehensively covers the catchment population; because of the geography of the catchment area all patients in the area are admitted to one of the three hospital sites of East Kent Hospitals University NHS Foundation Trust (EKHUFT); the population in East Kent is older in comparison to the United Kingdom average; and finally, use of the LaFrance methodology will also increase the reported incidence.

This current study clearly demonstrates that patients with AKI, even after correcting for age, gender, co-morbidity, and CKD, have an increase in morbidity and mortality both in the short and long term in comparison to patients without AKI. These outcomes also hold true for small changes in serum creatinine (AKI stage 1).

In comparison with patients with no AKI those with AKI stage 1 had a 52% longer hospital stay (length of stay (LOS)), a 2.8-fold increased risk of admission to the intensive therapy unit (ITU), a 39% longer ITU stay (in those who went to ITU), and a 2.4-fold greater in-hospital mortality. Furthermore, patients with AKIN 1 had twice the long-term risk of death, a 33% higher likelihood of an increase in care, and a 42% higher risk of re-admission to hospital within 30 days.

In those patients with AKI stage 3 (the subject of the NCEPOD report)[100] hospital length of stay doubled, there was a 22 times higher risk of admission to ITU and ITU length of stay was also doubled, consistent with national data from the Intensive Care National Audit and Research Centre.[104] Acute renal replacement therapy (RRT) support was required in 13.1% of patients with AKI stage 3. Hospital mortality was 26-fold greater and in those surviving to leave hospital there was a 5.5-fold increased risk of subsequent death. Patients with AKI stage 3 had a 7% higher risk of requiring an increase in care and had a 54% higher risk of re-admission to hospital within 30 days than patients with no AKI.
In terms of chronic RRT, 0.45% of patients with AKI and 3.40% of patients with AKI stage 3 subsequently required chronic RRT.

In terms of length of stay, as the time of entry into the cohort was the date of admission for each patient there is the possibility of reverse causality, for example a patient who has a longer length of stay may have a greater risk exposure to the development of AKI. However, in this cohort, of the 5,521 admissions with AKI, 4,064 (73.6%) already had AKI on admission.

Strengths and weaknesses of study

The population-based analysis reported here considers all patients admitted in a general hospital setting in the United Kingdom during a 6-month period. The catchment population for this cohort is from East Kent in the South East Coast of England. In comparison to the wider population in England East Kent has an older population (mean age 42 years compared to the national mean age of 39)

but with fewer ethnic minorities (6.3% of Black and Ethnic minority compared with 14.6% nationally).[105] Nevertheless, data linkages between the pathology, hospital data warehouse, renal and intensive therapy unit systems have enabled the study described here to come closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date.

However, this study is a retrospective database study and clearly has limitations that need to be recognised and addressed. Key to the definition of AKI is knowledge of pre-morbid kidney function (baseline serum creatinine (SCr)) and the threshold value of SCr from which change is measured (reference SCr). The importance of baseline SCr is in the determination of pre-existing CKD and this value should be based on SCr values available > 3 months prior to the index event. The reference SCr should be ideally be the lowest SCr recorded within 90 days of the event to distinguish this value from the baseline SCr. However, practically in many cases there may be either few or no pre-hospitalisation SCr values making distinction between baseline and reference SCr impossible. This is an area that requires further guidance and consensus from the international community and various strategies have been suggested including varying the baseline/reference creatinine from admission to 365 days prior, [95] taking the average or median of values between 7-365 days prior to admission, [96] back calculating reference SCr for missing values from an assumed MDRD glomerular filtration rate of 75 ml/min/1.73m^2, [97] and (most recently) a method employing multiple imputation using known co-morbidity strengthened by factoring in the lowest admission SCr. [98] For simplicity this study used the lowest SCr in the 12 months prior to hospital admission to define AKI, and expressed this as the baseline serum creatinine. It may be that by employing this method the study has included patients with progressive CKD and defined them as AKI stage 1. However, as LaFrance et al demonstrated and the data in this study confirms, patients with AKI stage 1 using this methodology still have a significantly increased likelihood of a specific adverse outcome occurring compared to patients with no AKI. [95]

The lowest serum creatinine in the 12 months following discharge was utilised to categorise AKI (for those without pre-hospitalisation creatinine) in 8.2% of

admissions with AKI. It has to be acknowledged that the assumption that AKI was present if serum creatinine improved following admission by greater than 26.4 μmol/l may not always be correct but use of this methodology was only necessary in 8% of those categorised as having AKI. The incidence of AKI in admissions utilising a post discharge baseline (9.9%) was less than in those where pre-admission creatinine data was available (16.1%).

It is also not possible to be certain that none of the patients with insufficient SCr data experienced AKI. These patients were significantly younger and had less co-morbidity than those with sufficient SCr data and either had no SCr result prior to, or following hospital admission. Survivors (9,830 of 10,030) were also short stay patients (LOS 0-2 days) and were therefore unlikely to have sustained any degree of AKI. The 200 patients in this group who did not survive the hospital admission had a mean LOS of 13.5 days, lack of baseline SCr data precluded derivation of AKI status in these patients. AKI will therefore have been underestimated. This also raises the issue of possible ascertainment bias, that sicker patients may have more creatinine tests, increasing the probability of detecting AKI.

Co-morbidity data was extracted from the hospital data warehouse using validated algorithms, however this still relies on the accuracy of coding of clinical episodes (a well recognised problem of retrospective database studies), which may not necessarily be correct. This also applies to the analysis of increase in care on discharge, which relies on the accurate coding on the patient administration system (PAS) at time of discharge.

While the statistical models used in this analysis have accounted for multiple confounders identified in the literature to date there is always the possibility that there may be other confounders hitherto unknown.

Finally, despite the estimates here of the incidence of AKI in a typical general hospital setting being the highest to date, EKHUFT does not provide

cardiothoracic, liver or burns services and the reported incidence of AKI may still be an under-estimation of the total population incidence.

Conclusions

The data reported here comes closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date. Nine per cent of all admissions and 15 per cent of non-maternity and non-day case admissions to hospital sustained an episode of AKI with increased subsequent short and long term morbidity and mortality, even in those with AKI stage 1. What this study adds to existing knowledge is data enabling a much more accurate assessment of the overall impact of AKI on the healthcare economy. This study provides data concerning hospital and intensive therapy unit mortality, length of stay (LOS), re-admission and renal replacement therapy (RRT) usage. The study also details the rate of RRT after longer-term follow-up and the social care impact in terms of increased level of care in those surviving an episode of AKI. These increased adverse outcomes from AKI confer an increased burden and cost to the healthcare economy. The data presented here enables this cost to be quantified (see below) and will furnish a baseline for quality improvement projects (including those described subsequently in this thesis) aimed at early identification, improved management, and where possible prevention, of AKI.

It has been suggested that milder forms of AKI defined by creatinine criteria may simply represent a marker of general system pathology and multi organ dysfunction, not specifically related to kidney injury per se. Whether this is true or not, AKI defines a group of patients whose outcomes are poor, both in the short and long term, who are sub-optimally managed, and who should represent a focus for patient safety improvement.

With the international agreement on the definition of AKI and its validation in clinical research, it has become clearer how important the effective management and prevention of AKI is. Agreed definitions have provided a comparable

platform for the audit of AKI and its management and outcomes, both in hospital and in the community.

Economic Impact

Following on from the study reported here, in collaboration with Marion Kerr (Health Economist) at the Department of Health, the data sources and analyses here were used to inform a health economic analysis of the short and long-term impacts on quality of life and healthcare costs. Both national data in the form of Hospital Episode Statistics (HES) for the National Health Service (NHS), and data warehouse and laboratory data from East Kent Hospitals University NHS Foundation Trust (EKHUFT) were used in regression analyses to estimate the impact on mortality and length of stay in hospital, and a Markov model (developed by Marion Kerr) was used to estimate the impact on quality-adjusted life years and NHS costs. [106] (See Appendix 3: Paper 3: The economic impact of acute kidney injury in England)

The results of this study suggested the annual number of excess inpatient deaths, with AKI in England may be greater than 40,000, [106] and the annual cost of AKI-related inpatient care in England is estimated at £1.02 billion. [106] (See Appendix 3: Paper 3: The economic impact of acute kidney injury in England)
The results of this study received significant media attention and have aided the political drive within the NHS to improve the management of acute kidney injury.

Chapter Summary

This study reports an incidence of acute kidney injury (AKI) in the 6 month period of 15,325 pmp/year (adults) (69% AKI stage 1, 18% AKI stage 2 and 13% AKI stage 3). In-hospital mortality, length of stay and ITU utilisation all increased with severity of AKI. Patients with AKI had an increase in care on discharge and an increase in hospital readmission within 30 days.

The data reported here (and published in the academic literature – see Appendix 2: Paper 2: What is the real impact of acute kidney injury?), comes closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date. Fifteen percent of all admissions sustained an episode of AKI with increased subsequent short and long term morbidity and mortality, even in those with AKI stage 1. This confers an increased burden and cost to the healthcare economy, which can now be quantified, and has been in a subsequent publication (see Appendix 3: Paper 3: The economic impact of acute kidney injury in England). These results will furnish a baseline for quality improvement projects aimed at early identification, improved management and where possible prevention of AKI. The publication of these papers led to considerable debate within the media, the medical community, and at a high level within the Department of Health. Following this NHS England released a patient safety alert (Stage Three: Directive) mandating that all Trusts in England alert to AKI, and with this delivered a standardised algorithm for the detection of AKI (see Appendix 9).

Following this work the AKI National Programme developed the "Think Kidneys" quality improvement partnership to raise awareness of and improve the management of AKI.

Chapter 3: Develop alerting to AKI

From the epidemiology presented in Chapter 2 we know that acute kidney injury (AKI) is a common problem in hospital with significant morbidity and mortality, and the NCEPOD report [100] tells us that AKI is both poorly recognised and then subsequently managed by clinicians. Now the problem is evident and clearly defined, the first stage therefore in improving the management of AKI is to alert clinicians to its presence as soon as possible. This early recognition will allow optimum management and effective intervention to be instigated early in the disease process in order to improve outcomes in terms of morbidity and mortality. This aids the "early management" documented in Figure 6 in Chapter 1.

In terms of diagnosis of AKI, as previously discussed, this involves the comparison of the present laboratory serum creatinine (SCr) to a baseline result for a given patient. This is therefore the comparison of one numerical result to another, a process which does not require human intervention and can be automated by a computer. In this way AKI lends itself to automated clinical alerting, and by doing this removes the necessity of the clinician to define whether a patient has AKI or not.

Aims

The aim of this chapter is to develop alerting of patients with acute kidney injury, to provide early recognition and support early effective management interventions in these patients.

Daily AKI report – Static Alert - Methods

With this in mind a daily report of patients with AKI at East Kent Hospitals University NHS Foundation Trust (EKHUFT), a system named SAKI (Stop Acute Kidney Injury) was developed. Each morning all creatinine tests performed and recorded on the East Kent pathology database from the previous day are downloaded from the pathology server to the secure 'AKI Database'. The

database already contains all creatinine results from the last 12 months. The alert program defines acute kidney injury (as described in Chapter 2) by comparing the creatinine result from the previous day, with the lowest creatinine in the database for that patient in the last 12 months (taken as the baseline), in order to calculate the stage of AKI (using the Acute Kidney Injury Network (AKIN) criteria to define acute kidney injury). [89] The stage of AKI is then stored in the database. This result along with the previous creatinine results, and demographics for each patient with AKI, are placed in a view table that is made accessible to business intelligence software (a product called Qlikview, (Qlik.com) was used) for reporting. Qlikview is business intelligence software that allows web browser based data reporting. Qlikview is deployed on the intranet at EKHUFT and accessible via a secure login.

The SAKI system therefore provides a report of all inpatients at any of the three hospitals (Kent and Canterbury Hospital (KCH), William Harvey Hospital (WHH) and Queen Elizabeth the Queen Mother Hospital (QEQM)) of East Kent Hospitals University NHS Foundation Trust (EKHUFT) who have acute kidney injury, defined from the previous day's bloods results. This provides the first step of alerting to the presence of acute kidney injury (AKI) to achieve recognition, however the NCEPOD [100] report was clear that even after recognition of AKI, it is subsequently poorly managed by clinicians.

The next step is therefore to provide standardized investigation and management pathways (treatment pathways) to guide clinicians in the management of these patients following the recognition of AKI.

Treatment pathways

Alongside the report of patients with AKI, an AKI treatment pathway (to ensure standardised effective assessment, investigation and management of AKI) (Figures 9,10,11), an AKI referral protocol (to ensure timely referral to renal, urological and intensive care services) (Figure 12), and an AKI transfer policy (ensuring safe inter-hospital patient transfer in a patient with AKI) (Figure 13) were developed based on and modified from policies from the London Acute

Kidney Injury Network (LAKIN; http://www.londonaki.net) and posted on the website alongside the AKI report. The LAKIN treatment pathways were employed as they had already been ratified by Trusts across London and by using these pathways across East Kent provided further standardisation of care.

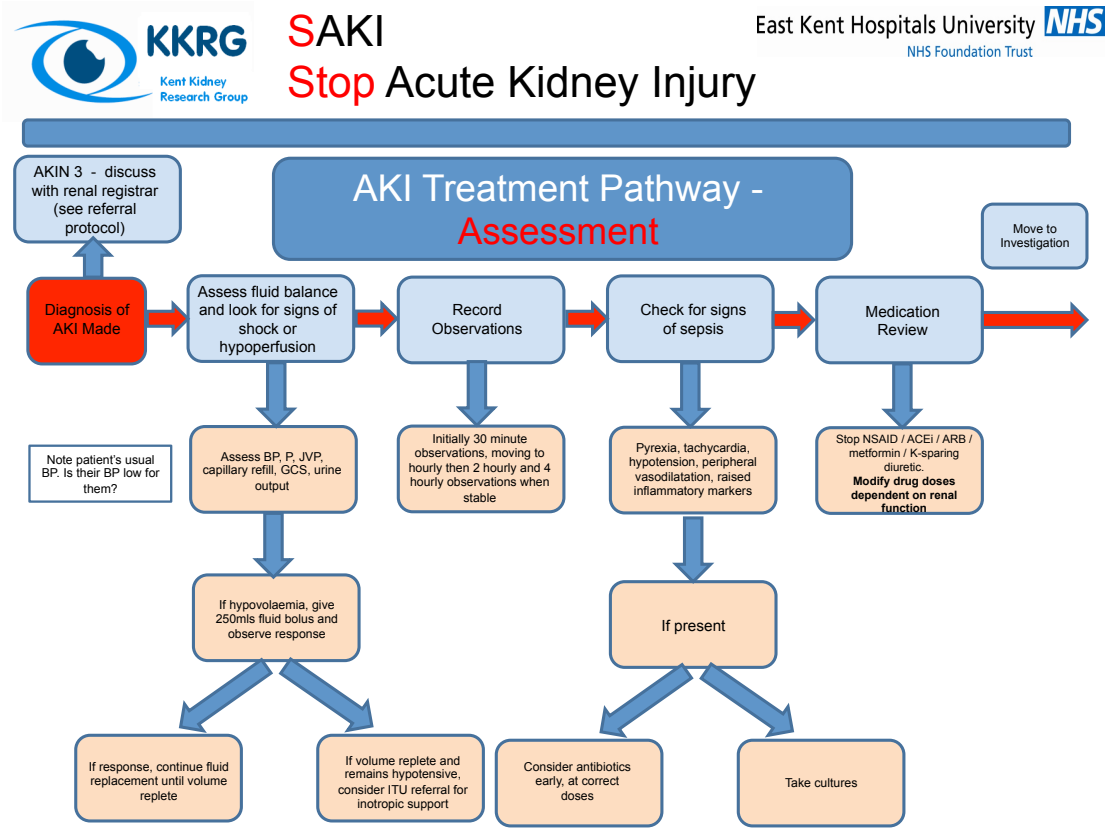


Figure 9: AKI Treatment Pathway: Assessment: The initial assessment of a patient with acute kidney injury (AKI).

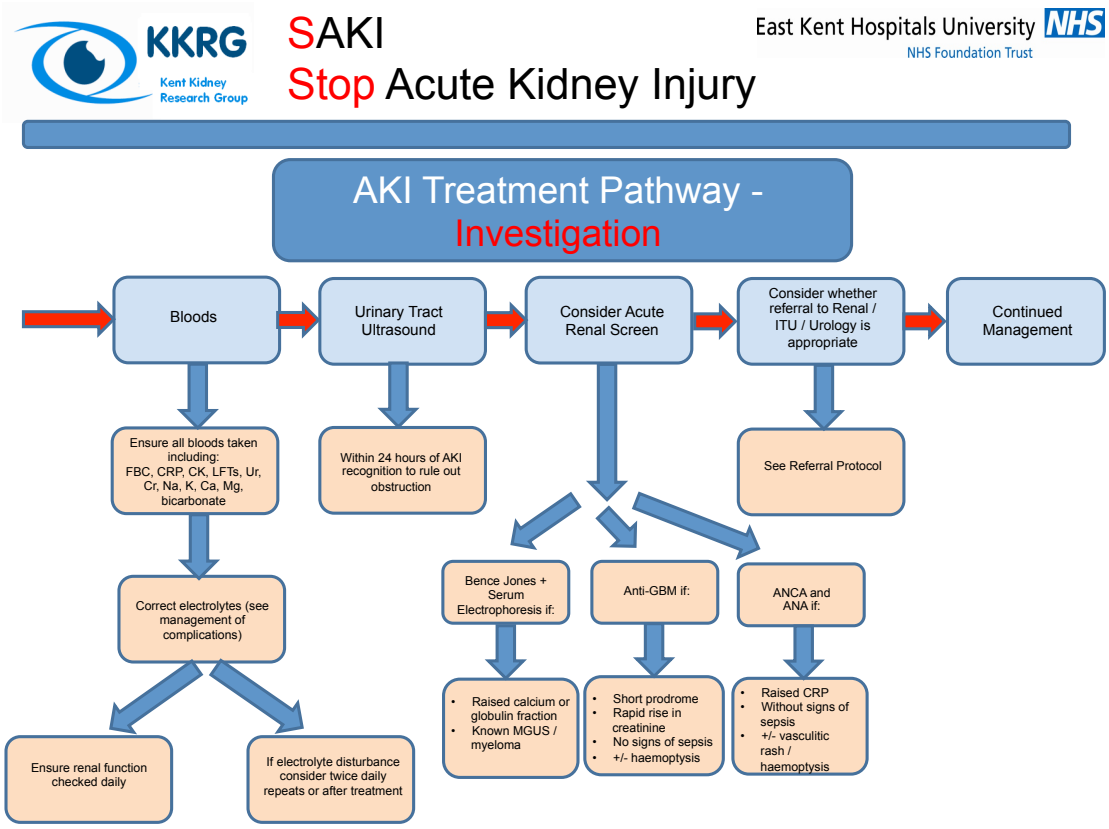


Figure 10: AKI Treatment Pathway: Investigation: The investigation of a patient with acute kidney injury (AKI).

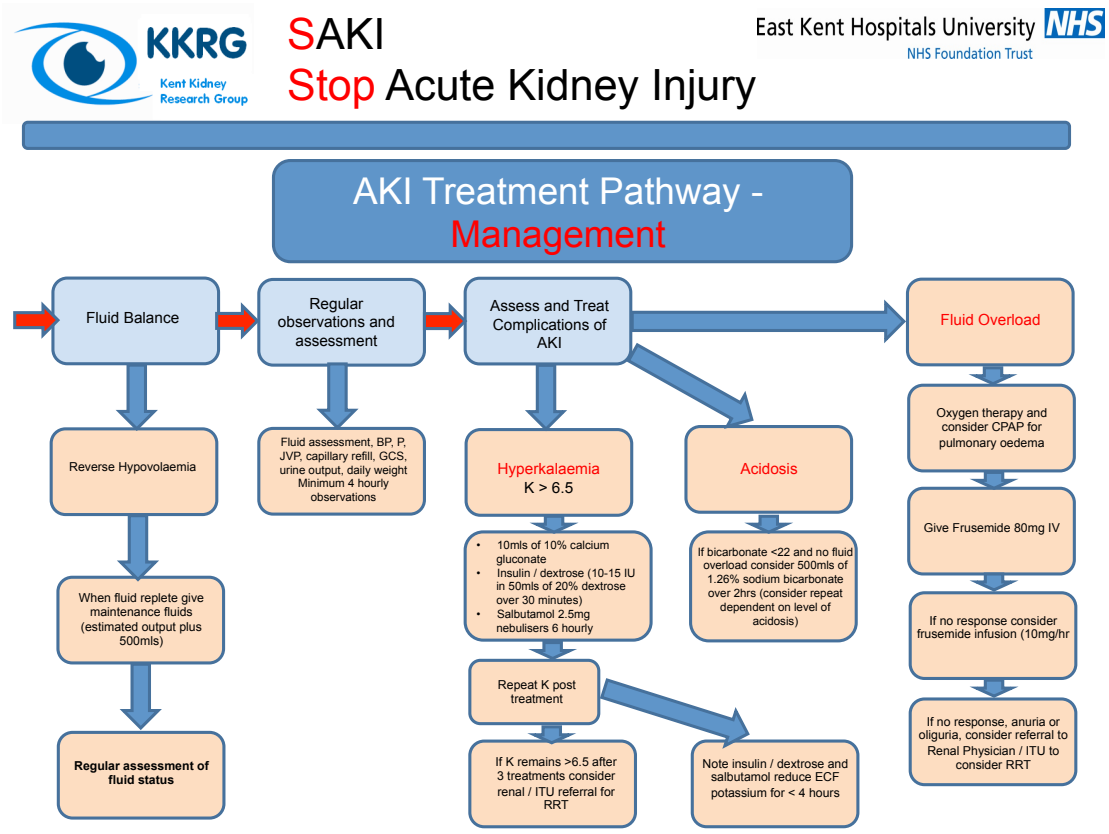


Figure 11: AKI Treatment Pathway: Management: The management of a patient with acute kidney injury (AKI), and the complications of AKI.

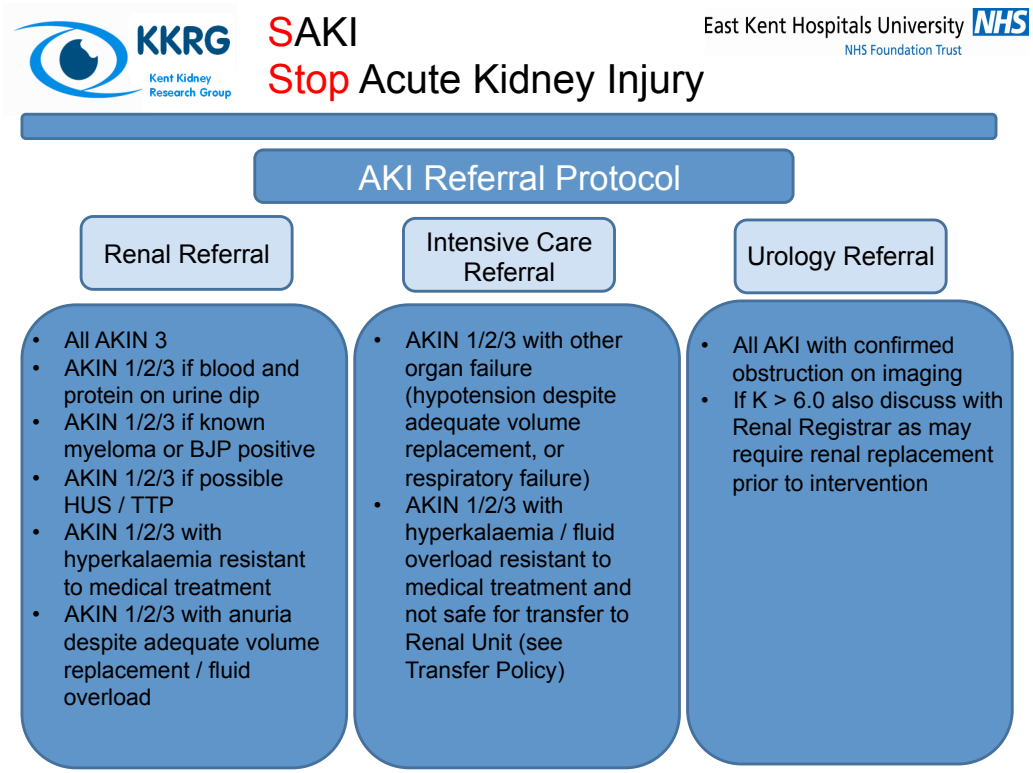


Figure 12: AKI Referral Protocol: A referral protocol to define when and to whom a patient with acute kidney injury (AKI) should be referred.

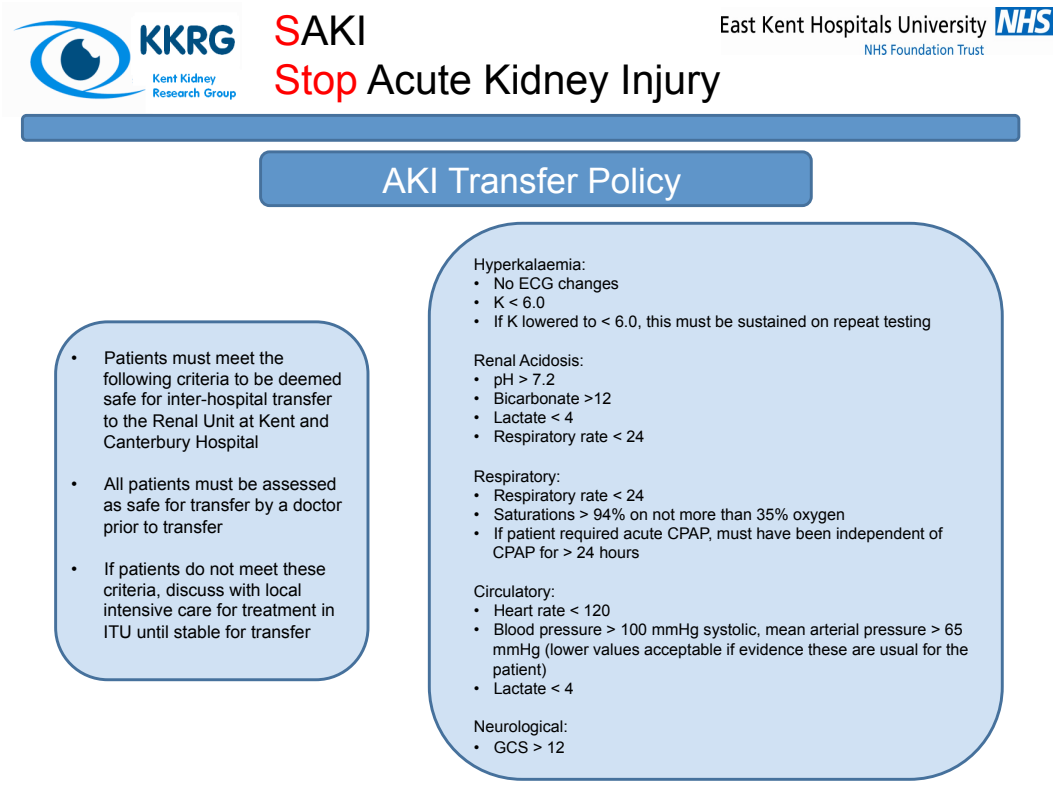


Figure 13: AKI Transfer Policy: A transfer policy for patients with acute kidney injury (AKI) to define whether they are safe for inter-hospital transfer.

Data Presentation - Results

Via the Qlikview reporting system on the Trust intranet, the AKI alert system has several pages / tabs to provide information on all patients currently an inpatient at the 3 hospitals of EKHUFT, who have acute kidney injury. This provides information such as patient demographics, ward location, stage of AKI, and previous blood results per patient to allow confirmation of AKI and to view the development or recovery of the AKI. At a specialist service provision level, it also allows a view of AKI within EKHUFT at any given time.

The data pages are as follows:

Main Menu

The main menu allows navigation between the different reports of the SAKI AKI alert system. The following screenshot (Figure 14) demonstrates this menu:

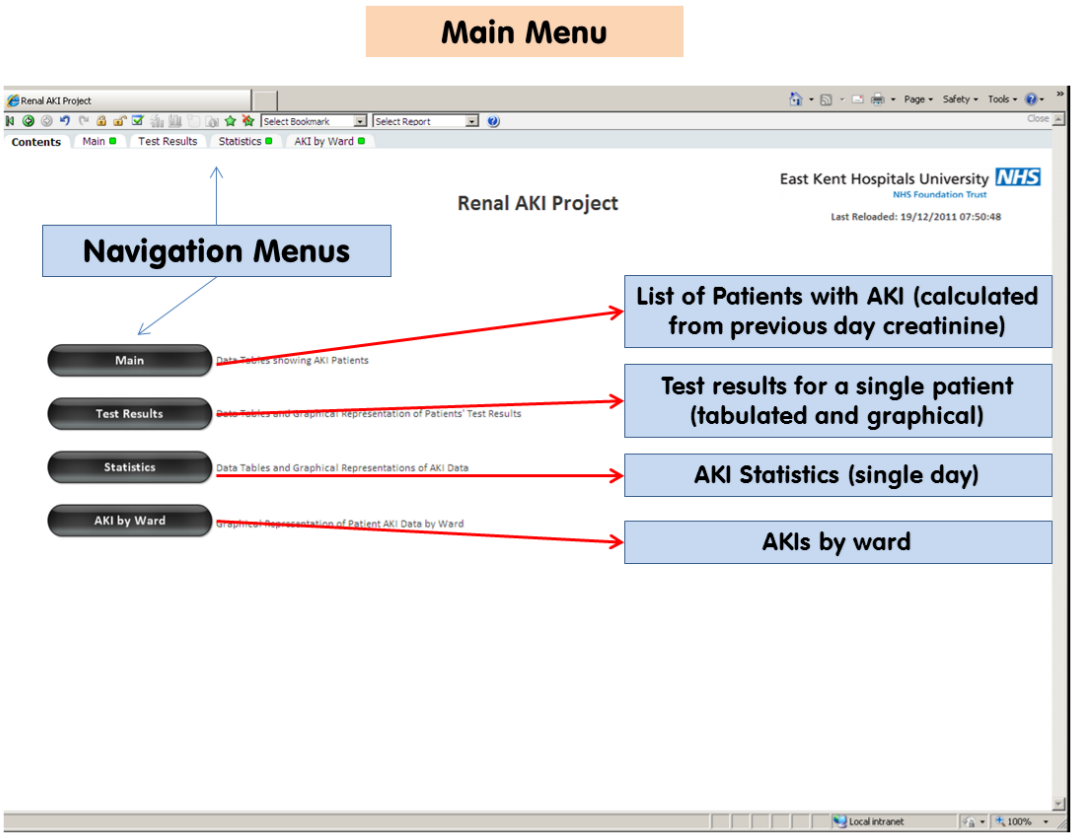


Figure 14: SAKI AKI Alert System: Main Menu.

AKI Patient List

The main page of the report (Figure 15) documents all of the patients with AKI (based on the creatinine result from the previous day) at EKHUFT. The system calculates the stage of AKI (using the AKIN criteria described previously) by comparing the creatinine result from the previous day with the lowest creatinine in the prior 12-month period. The table shows the patient's demographics followed by their stage of AKI and the current and baseline creatinine results. For each patient there is also the consultant responsible for the patient's care.
The modality column documents whether the patient is already known to the renal service, and what renal clinic they attend, for example the general nephrology clinic, or the transplant clinic.

By clicking on the filter tables at the top left of the screen, the lower table of patients can be filtered by specific groups for example by; hospital, AKI stage, ward or consultant. It is possible to search for a specific patient using the search box on the page. By clicking on a specific patient, this then filters the following pages to just the data for that patient.

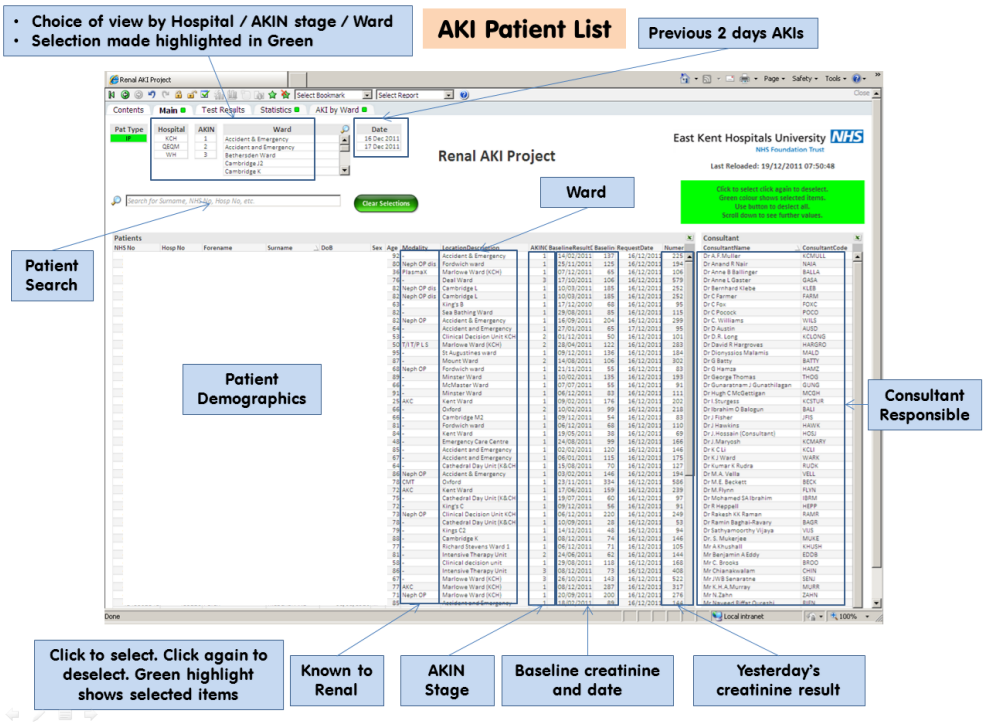


Figure 15: SAKI AKI Alert System: The Main Page - all patients at EKHUFT with AKI.

Test Results

Once a single patient has been selected on the "AKI Patient List" page, by opening the "Test Results" page (Figure 16) the results specific to that patient are displayed. At the top of the page are the demographics for that patient. Below this is a graphical representation of the patient's results over time, along with these results in tabular form to the right of the screen. By clicking the "clear selections" button, this de-selects the patient and allows the selection of another patient on the "AKI Patient List" page. It is also possible to search for a specific patient using the search box.

Figure 16: SAKI AKI Alert System: Test Results Page – once a single patient is selected on the main page, this shows all the creatinine results for a given patient over time, both in a tabular and graphical form.

Statistics

The "Statistics" page (Figure 17) reports graphically the number of patients with AKI by hospital and by ward at EKHUFT. This allows an overview of AKI at EKHUFT at any given time, to aid with specialist intervention and guide service delivery planning.

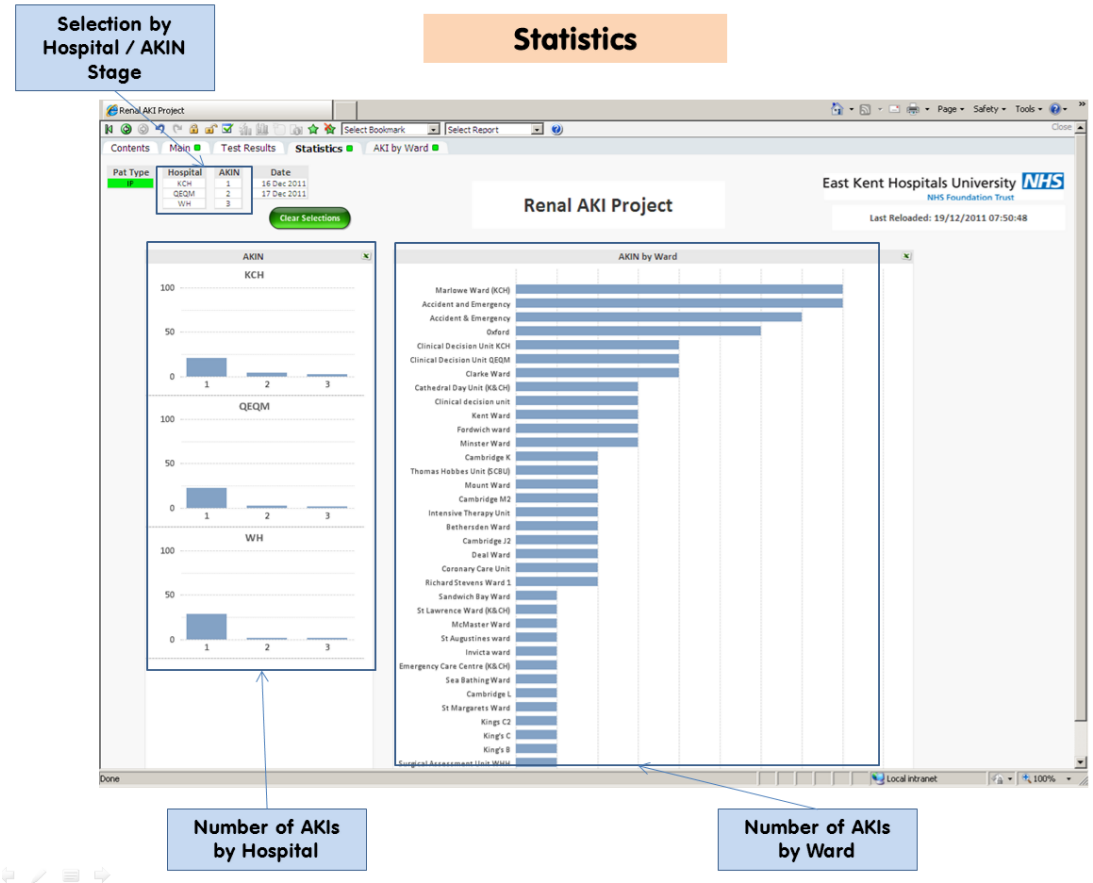


Figure 17: SAKI AKI Alert System: Statistics Page - an overview of AKI at EKHUFT at any given time, by hospital, ward, and stage of AKI.

AKI by Ward

The "AKI by Ward" report (Figure 18) documents the number of AKIs on each ward at EKHUFT. The patients with AKI stage 1 are shown in yellow, AKI stage 2 in orange and AKI stage 3 in red. By clicking on a specific ward and then on the coloured bar (stage of AKI) of interest on that ward, the specific patients with AKI on that ward are displayed in the table on the right.

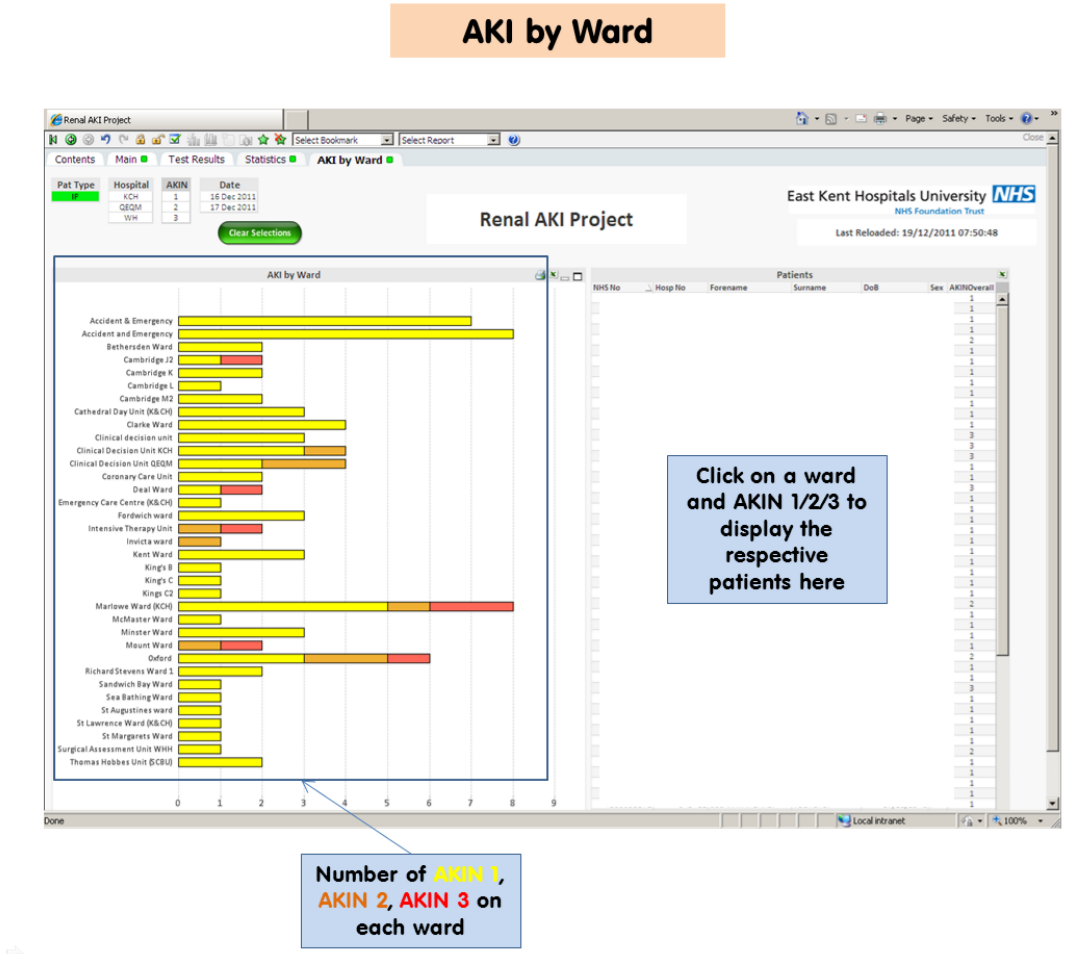


Figure 18: SAKI AKI Alert System: AKI by Ward Page. AKI stage 1, are shown in yellow, AKI stage 2 in orange and AKI stage 3 in red.

Clinical intervention

With the developed AKI report and agreed management protocols for AKI the next question is who to deliver the information to, in order to efficiently intervene in a patient's care and ensure adherence to the above protocols to ultimately improve the morbidity and mortality of patients with AKI. While the obvious answer would be the junior doctors responsible for a patient's care, at the time of deployment of SAKI there was little understanding and appreciation of AKI by junior doctors, as evidenced by the findings of the NCEPOD report, [100] and they moved from one rotational job to the next every 3-4 months. The decision was therefore made to provide education sessions to the junior doctors in order to begin to raise awareness of acute kidney injury, but deliver the AKI report to the critical care outreach nurses and the renal consultants. Figure 19

shows a pictorial representation of how the SAKI AKI alert system worked in terms of data flow and clinical intervention.

Small focused educational sessions were delivered to the critical care outreach nurses at each of the 3 hospital sites of EKHUFT, both to educate on the assessment, investigation and management of acute kidney injury, but also the use of the SAKI AKI reporting system. The critical care outreach nurses were thought to be ideal to both assess and provide management advice for the patient with AKI, but also in doing so deliver education at the point of care to the nursing and medical staff looking after the patient. In the year 2000 the Department of Health published the report 'Comprehensive Critical Care' [107] which was a catalyst for the development of the role of the critical care outreach nurse to support the nursing and medical staff on the wards to ensure recognition and optimum management of the unwell patient, with early escalation to intensive care as necessary. This role therefore fits in neatly with the management of acute kidney injury, for a number of reasons. Firstly, as discussed at the end of the last chapter it has been postulated that especially in the milder forms of acute kidney injury, AKI is a marker of general system pathology and multi organ dysfunction rather than being specifically related to kidney injury. Therefore, AKI in this respect could be seen as an alert system in itself, identifying the unwell patient, and hence directing the critical care outreach nurses to the unwell patients on the ward that may need intervention and escalation of care, in the same way that an early warning score (EWS) based on vital signs of the patient is used to do so. Secondly the core management of a patient with AKI includes assessment of fluid status, and optimisation of blood pressure and oxygenation, which are sometimes not achieved in the management of AKI on the ward as evidenced by the NCEPOD report, [100] but for which the critical care outreach nurses are highly trained in achieving as part of their assessment and management of the unwell patient.

It was agreed that all patients with AKI stage 2 would be reviewed by a critical care outreach nurse at any of the 3 hospital sites of EKHUFT. Following clinical assessment of the patient a clear management plan (following the AKI treatment

pathway in Figures 9,10,11) would be documented in the patient's medical notes and the clinical team informed of the plan, and thereby also delivering education to the point of care on the management of AKI. For each patient reviewed, details are also documented on the AKI audit form online, which is completed each time a patient with AKI is reviewed (Figures 20,21,22). This not only allows accurate audit of patients with AKI, but also allows reporting of these details back on to the SAKI AKI report for each patient. Therefore, the next day, when the patient may be present on the AKI alert report again (as the AKI remains), the plan given for the previous day will be reported and can be updated with each subsequent review. The patients are reviewed as deemed necessary with all interactions documented in both the medical notes and the AKI audit form online. The critical care outreach nurse contacts the renal registrar for advice as necessary, and following discussion the decision is made regarding appropriate transfer to the Kent Kidney Care Centre at Kent and Canterbury Hospital, in line with the AKI Referral Protocol (Figure 12) and AKI Transfer Policy (Figure 13). The critical care outreach nurse also liaises with the Intensive Therapy Unit (ITU) as required.

To provide an additional alert within the clinical notes (and also to aid with clinic coding and later notes audit), the critical care outreach nurse places a sticker in the notes (Figure 23). This sticker has several functions:

- Alerting the clinical team when reviewing the notes that the patient has AKI
- Providing generic advice for the investigation and management of patients with AKI
- Documenting the contact details of the renal specialist team so that further specialist advice can be sought as necessary
- Providing an address and QR code for a website providing education for the clinician on the investigation and management of AKI

For all patients with AKI stage 3, the decision was made that the renal consultant on-call would telephone the clinical team looking after the patient, both to gain further information and to provide specialist advice on management. The patient

is then reviewed if required. If appropriate, transfer to Kent Kidney Care Centre is arranged. Patients with AKI stage 3 are the most likely to need specialist intervention in terms of invasive investigations such as renal biopsy, and specialist management in terms of renal replacement therapy (RRT). Hence the intervention of the renal specialist in all cases of AKI stage 3 to ensure timely specialist intervention, investigation and management. Again the renal consultant documents the intervention in the same method as the critical care outreach nurse.

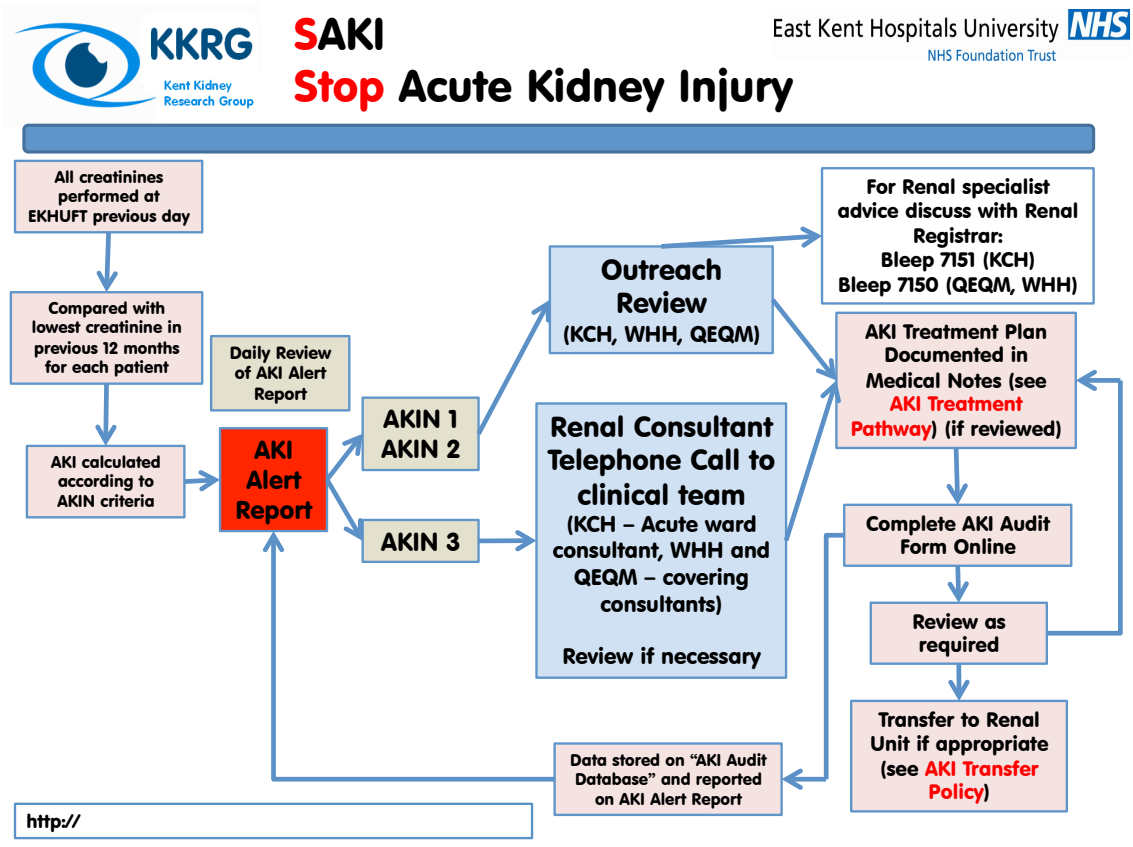


Figure 19: The SAKI AKI Alert System – data flow and clinical intervention.

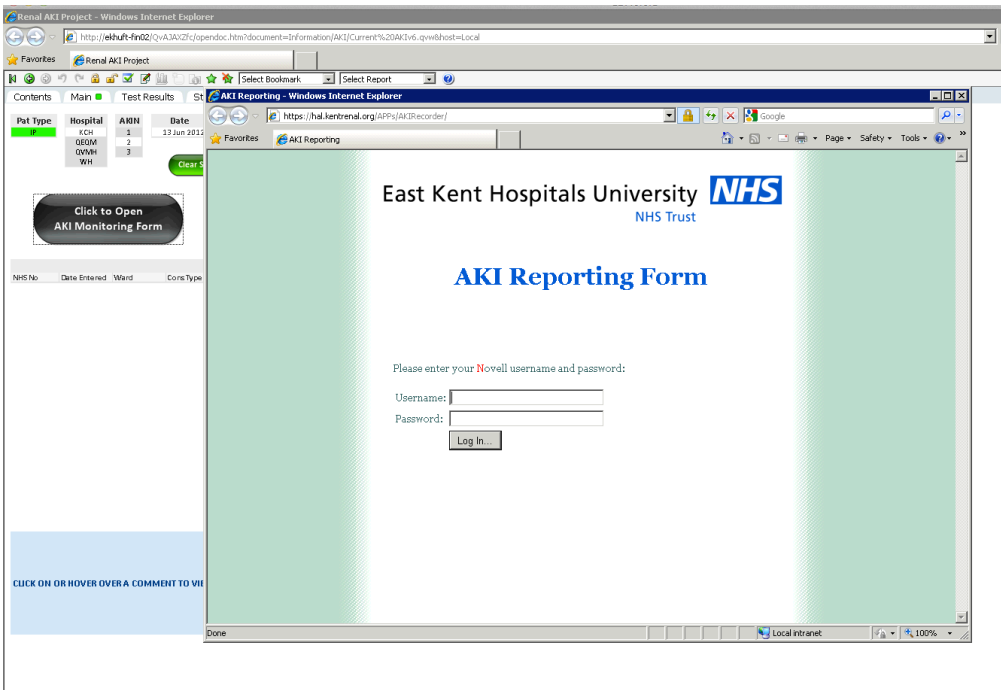


Figure 20: The access portal to the AKI audit form to document the review of patients with AKI.

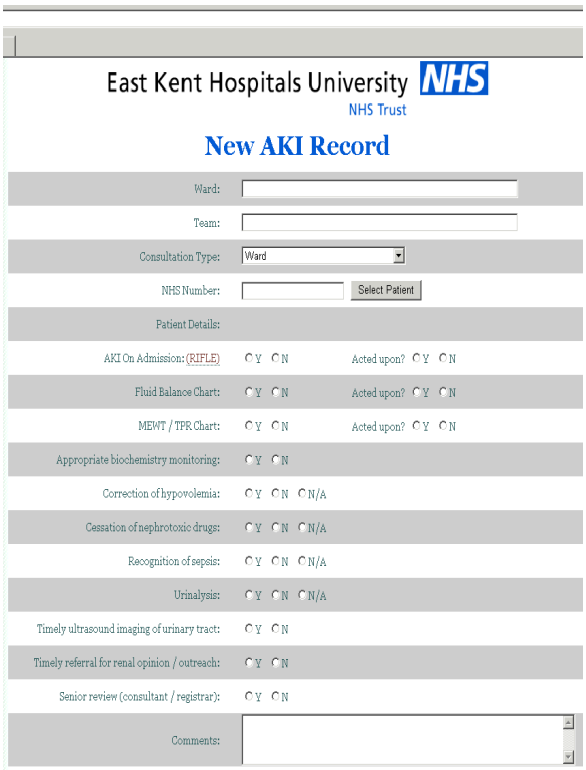


Figure 21: The AKI audit form

An audit form to capture the review of the patient with AKI and from the comments (then upload to and visible on the SAKI AKI alert system) provide continuity of care for the following review of the patient.

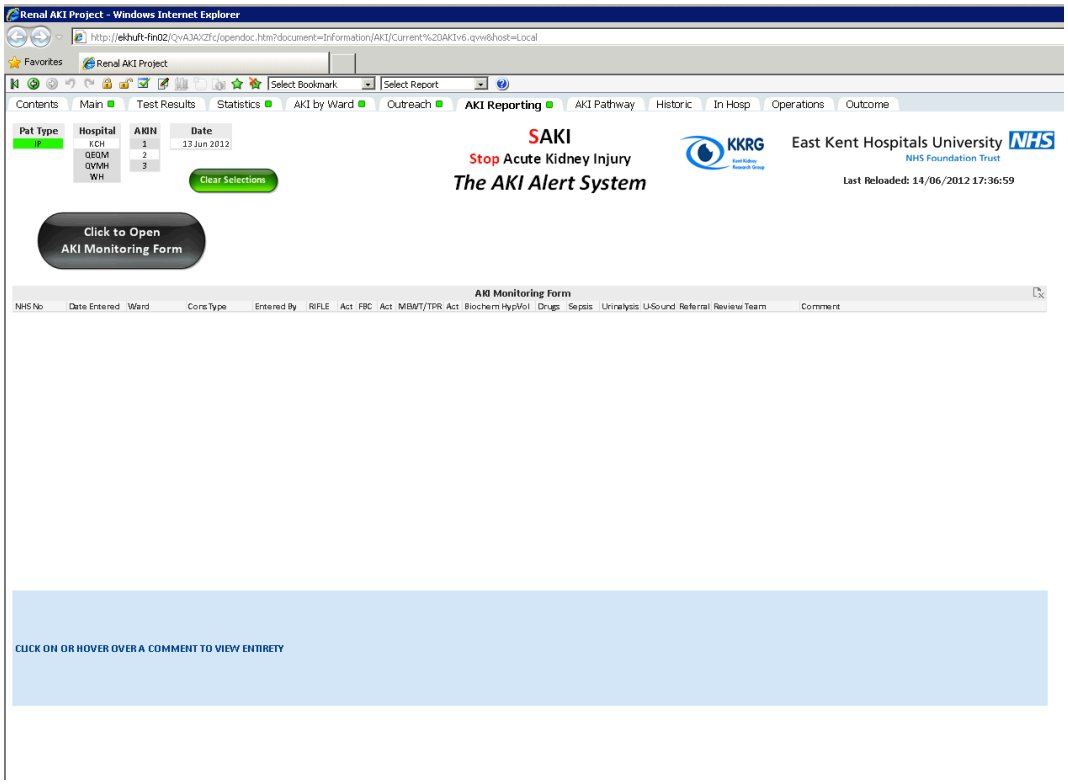


Figure 22: The visualisation of the comments from the AKI audit form, back in the SAKI AKI report to provide continuity of care and easily visualisation of previous reviews.

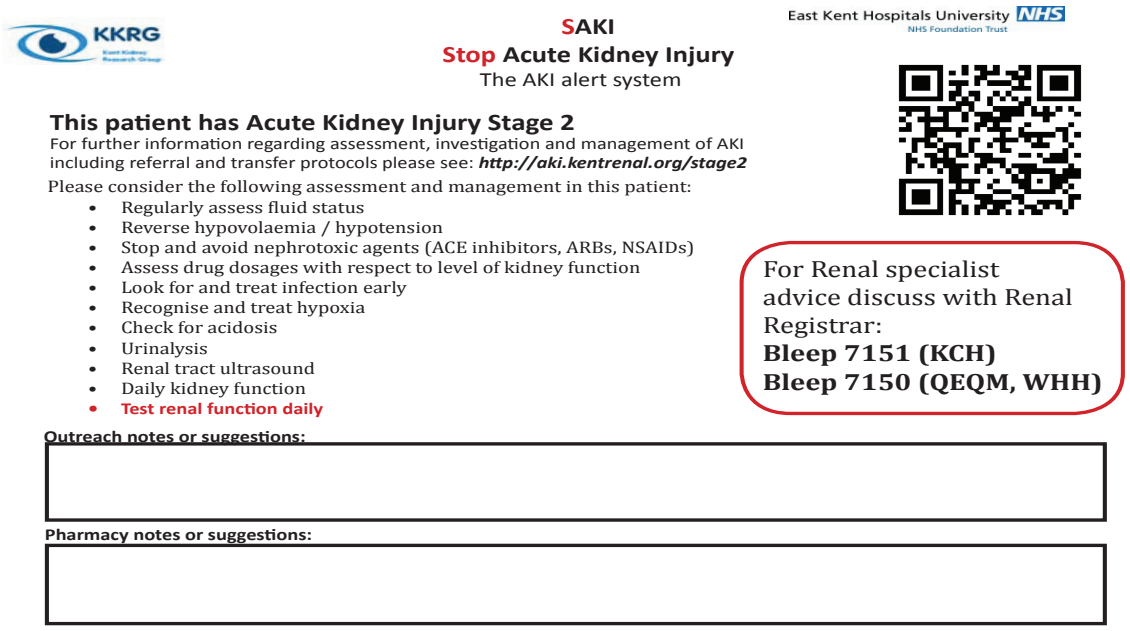


Figure 23: An example of a sticker placed in the patient's clinical notes to alert to AKI

Integrating alerting into clinical care – a qualitative analysis

Introduction

With development of Information Technology (IT) and greater access to electronic data within healthcare, there is a great opportunity to deliver data in the form of clinical information both efficiently and effectively to the clinical team. This can be taken one step further with the use of a clinical decision support system (CDSS) as with the SAKI AKI alert system above, which can use clinical data to provide advice on clinical management, using and ensuring compliance with locally or nationally agreed clinical guidelines. As well as effective intervention in clinical care, this also allows the standardization of care.

However, the key to success of an alert system or clinical decision support system is the effective integration into clinical care, with user adoption and active use of the system. Although there has been work to predict whether users will embrace a new IT system, this has mainly assessed communication between clinicians, result reporting, clinical documentation and ordering of investigations. There has been less evaluation of the delivery of a clinical alert system or CDSS. A clinical alert system or CDSS has the ability to significantly improve clinical practice and patient safety, providing value to the patient, but at the same time may challenge a clinician's current management. Some clinicians may embrace this challenge and welcome advice, however others may perceive an attack on their clinical management abilities. The potential value of a clinical alert system or CDSS will not be realized without user acceptance and adoption.

The SAKI AKI alert system was implemented at EKHUFT as described above, to provide alerting to the critical care outreach nurses of patients with AKI stage 2, and alerting to the renal consultants of patients with AKI stage 3, to provide early intervention in AKI. The next stage of this project was then, following the development of accurate risk models to predict which patients would develop

new AKI (to allow earlier intervention in the disease process to ultimately prevent AKI), or worsening AKI if already present (Chapter 5), to add alerting to patients at risk of developing AKI to the SAKI AKI alert system. The SAKI AKI alert system would then encompass AKI and AKI risk alerting. However before progressing further with the development of alerting to include alerting to risk, it was key to ensure that the correct method of alert delivery and clinical intervention was achieved. This would however only be the case if there is sufficient user acceptance and adoption. Therefore, the next step here focuses on what barriers exist to the introduction and integration of a clinical alert system or CDSS into clinical care, and using qualitative research methods investigate how this can be successfully achieved in the setting of AKI, initially at East Kent Hospitals University NHS Foundation Trust (EKHUFT), but also looking to dissemination across the National Health Service (NHS).

IT in Healthcare

With increasing processing power of computing devices, proliferation of the internet, mobile and smartphone devices, and our ability to access information in real time, comes a change in our expectations of information delivery and communication in healthcare. With access to electronic information systems at the point of care, we have the potential to inform clinical decision-making, improve efficiency, quality and standardisation of healthcare, and provide a patient-centred approach.[108,109]

The 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the setting of acute kidney injury (AKI) highlighted systematic failing of identification and subsequent management of AKI in hospital. [100] As AKI is diagnosed by a change in a blood test, which can be processed electronically by a computer program, as already suggested this is an excellent example of where IT can significantly impact on patient care.

There have been several studies demonstrating effective use of IT in healthcare including reducing admissions to hospital, improving safety, reducing adverse clinical events and clinical errors, and also improving business efficiency. [110-115]

However, even with these advances, health care professionals often do not have access to real-time patient information at the point of care.

In order to provide the most value to patients and improve clinical practice and patient safety, an IT solution must be delivered to the correct person at the correct time. Picot et al [116] suggest that value to patients is not created directly by the IT solution, however it allows effective integration of a process into clinical care, which then provides value. Within all specialities in healthcare there are clinical practice guidelines (CPGs) to assist physician and patient decisions along appropriate management pathways. [117] We know however that these are not followed effectively in clinical practice. [118,119] With the development in technology, the computerization of CPGs has taken the form of computer interpretable guidelines (CIG), [120] computer executable guidelines (CEG), [121] and integration within an electronic health record. [122] Clinical decision support systems (CDSSs), through patient specific advice, can be used to inform and enforce management pathway guidelines. Previously, computerisation of CPGs have been technology driven. [121] However there is the need to actively involve the user in design and delivery of the system.

Although benefits of electronic alert and CDSSs may be apparent, there have been barriers to their introduction and utilization within healthcare. One of these barriers is user (in this case physician) adoption, also described as technology acceptance. [123]

Barriers to and Physician Acceptance of IT in Healthcare – User Adoption

Keys to successful integration of an IT solution into routine use are user acceptance, [124,125] and often a determinant of this, hospital information system design. [126-128] Yarborough and Smith suggest there are three main barriers to acceptance by physicians: organizational, information system (technology), and personal (human). [129] Van der Meijden et al suggest that satisfaction with the use of an IT system leads to acceptance. [130] Chen and Hsiao suggest that top management support, project team competency, system quality, perceptions of

usefulness and ease of use, affect acceptance by physicians. [131] When users of the system perceive that a system is useful, provides clinical utility and adds value, they develop a positive attitude towards the system, leading to user satisfaction and acceptance. [132-134] Dünnebeil et al suggest two opposing groups of physicians, those who embrace new technology within their clinical practice, and those who reject it. [135] They also report no significant difference in behaviour for different age groups or fields of specialization. [135]

In Germany there has been extensive work to develop a nation-wide telemedicine infrastructure to enable electronic healthcare. [136] Although physicians may agree on its advantages, [137] the programme has been delayed, primarily due to physician resistance. [135,137-139] This position is echoed across the European Union. [110] Reasons thought to underlie resistance are: the scale of work required for delivery and implementation, a disappointment with performance, and importantly concerns regarding privacy. [139]

Spil et al. suggest that user characteristics determine adoption of the system. These characteristics are determined by: relevance, resources, requirements and resistance. [140] Margreet Michel-Verkerke suggests that adoption is not a dichotomous phenomenon. [141] When clinicians are mandated to use a system, this does not ensure satisfaction and effective use. [141] This may lead to inaccuracies in data recording and data quality. Quality of the system and quality of the information the system delivers, are also important in ensuring user satisfaction. [142]

IT, Data Quality and Communication

Venkatesh and Davis define quality as the degree to which the user has the belief that a system performs its tasks well. [143] Spil, Schuring and Michel-Verkerke as part of the USE IT framework, describe the quality criteria of an innovation as: timeliness (accessibility), accuracy (informativeness) and ability to integrate. [140] Delen and Rijsenbrij suggest that quality is related to: correctness, up-to-dateness, accuracy, completeness and verifiability. [144] The quality of the information the system provides is paramount to the healthcare user. [141] Users

also value retrieving data above that of data entry, however data entry informs the information retrieved. Physicians place emphasis on the availability of complete, correct and relevant patient data, anywhere, and at any time. [145]

A successful IT system must integrate smoothly within the daily clinical activities of a healthcare professional, and the clinical management pathway of the patient, providing the correct information at the correct time. Pirnejad et al demonstrate that when a system does not provide clinical integration, for example does not support collaboration between physicians and nurses, physicians develop workarounds to the system. [146] These workarounds create inconsistencies in information, affecting data quality, reliability, and adversely affecting patient safety. [146]

Quantity is linked to quality of data. "Drowning in information, but thirsty for knowledge" suggests on one hand there is too much information, while on the other people complain of too little. They suggest the solution lies in information structuring. [113]
Information quality is also linked to its communication. Failure in communication, often due to inadequate information, is a common cause of adverse events and clinical errors. [147,148]

This all said, studies of a Nursing Information System have shown improvements in information quality and documentation. [149-152]

Methodologies for Predicting User Acceptance

Davis proposed a theoretical model to predict whether a user will accept the development and use of a new IT system, the technology acceptance model (TAM). [153] Perceived usefulness and perceived ease of use are two key factors in this model in relation to user acceptance. [153] TAM has been used to assess technology acceptance by healthcare professionals, [154-160] however the results have been inconsistent, likely due to the differing systems and user groups. [156,161]

Venkatesh et al extended the TAM with the Unified Theory of Acceptance and Use of Technology (UTAUT) model. [162] This was successfully tested in healthcare. [163]

Spil, Schuring and Micel-Verkerke introduced the USE IT theoretical framework for delivery of an IT system. [140] They suggest that user characteristics determine adoption of the system, and that these characteristics are determined by: relevance, resources, requirements and resistance. [140]

In the assessment of a clinical decision support system (CDSS) there is little work, however there is evidence that the perceived usefulness influences a CDSS, whereas the perceived ease of use does not. [155]

Summary

With development of IT and greater access to electronic data within healthcare, there is the opportunity to deliver clinical information systems and clinical decision support systems (CDSSs) to the point of care, to improve clinical practice and patient safety. However, the key to success of these systems is effective integration into clinical care, with physician adoption and active use.
Although there has been extensive work to predict whether users will embrace a new IT system, this has mainly assessed communication between clinicians, result reporting, clinical documentation and ordering of investigations. There has been less evaluation of the delivery of a clinical alert system or CDSS.

The work here (using qualitative methodology) will explore the effect of professional interactions, information sharing, and personal and professional characteristics on the use of electronic clinical information and clinical decision support. This work will aid and inform future implementations of such systems, and importantly inform the development of the AKI alerting system.

Methods

The qualitative analysis here, was designed by both Dr Michael Bedford and Professor Jenny Billings (Professor of Applied Health Research, University of

Kent). The focus group and interviews were conducted by Professor Jenny Billings and the analysis was performed by Professor Jenny Billings, with advice from Dr Michael Bedford. While the qualitative analysis process was designed by Dr Michael Bedford in collaboration with Professor Jenny Billings, and appropriate training undertaken by Dr Michael Bedford within the Certificate of Social Research Methods at the University of Kent, the decision was made for Dr Michael Bedford not to conduct the focus group and interviews or primarily analyse the resultant content. The reasoning behind this decision was so as not to introduce bias into the results, and ensure an objective and truthful view of the use of the AKI alert system in clinical practice at EKHUFT. I myself had implemented the AKI alert system at EKHUFT and both trained the Renal Consultants and Critical Care Outreach Nurses in the clinical use of the system, and provided education to the Critical Care Outreach Nurses in the investigation and management of AKI. Therefore if I was present at the focus groups or interviews the participants may not have felt able to speak openly about the system and this may have biased / influenced the content. Further, in the qualitative content analysis we felt that Professor Jenny Billings would provide a more robust and objective external assessment.

This qualitative study employed both focus group and individual interview design. Focus group method was used in this healthcare setting not only to expand ideas, but to gain consensus on views and promote good practice. [175] This particular research study promotes new and innovative ideas that may benefit from being explored within a group, particularly within a longitudinal approach. Variations in perception and experience will encourage deeper discussion and illuminate impacts, as well as reveal the nature and cause of practice changes in relation to the intervention. Individual semi-structured interview method, adapted for the Renal Consultant participants (as described in Chapter 3) allows clear structure of the topics to be covered but allows more flexibility and in depth discussion around these topic areas, which may not be possible within the group environment.

As above, the purpose of this was to inform and plan developments to the alerting system, adopting a user-involvement approach, using qualitative methodology to identify perceptions of the SAKI AKI alert system presently in place at EKHUFT and explore best communication and information pathways that will permit an alert system to both alert and provide actionable recommendations to clinicians for decision-making. This would allow accurate planning of a new / modified alerting system to include AKI and AKI risk alerting as described above, to ensure effective integration into everyday clinical practice.

Sample

The sample consisted of six renal consultants for the individual interviews and six outreach nurses who attended the focus group. All consultants worked across the three hospital sites within EKHUFT, and there was representation from all hospital sites from the outreach nurses. Consultants used the alert system to identify patients with the more serious AKI stage 3 and alert medical teams to offer advice and review if required, and outreach nurses identified AKI stage 2 patients and provided clinical review of the patient on the ward.

In terms of accessibility of the consultant and nurse groups it was established early on that different qualitative approaches would need to be used given their individual availability and potential to meet together. Consultants had to cover three sites and group meetings were difficult to convene, therefore interviews were the method of choice. Conversely, outreach nurses were difficult to capture individually but held a training session as a group once a month, and this provided an opportunity for a focus group. Tuning different methods to the requirements of the population group is considered good practice, in order to maximise attendance and enrich data. [164-167]

Instrumentation and data collection

For the focus group, a schedule was developed that explored perceptions of the impact on practice, aiming to identify best methods for delivering the alerts and recommendations. This covered aspects such as accessibility of information,

hardware, who the recipient should be (junior doctor, consultant), what form the alert should take (additional email, text), how to avoid alert fatigue and alerts being ignored. The focus group lasted one hour and was facilitated by Professor Jenny Billings an experienced researcher external to the clinical team. Interviews took place at a convenient time and location, carried out by the same experienced researcher.

The template and coding framework for both the focus group and interviews has been included in Appendix 5.

Data analysis

Data consisted of six 30-minute interviews and a one-hour focus group. These data were transcribed verbatim and subjected to a thematic analysis, using a pre-determined theme as an initial template for analysis derived from the interview schedule. Clinical team members were not involved in the data collection or analysis of the data; this was undertaken by Professor Jenny Billings, a researcher external to the clinical team. Regarding the interview and focus group schedules, sections 1, 2, and 4 were identical, however section 3 ('impacts on clinical practice and patients') was altered to account for the differing clinical roles in the project and communication experiences (i.e. with different people at different times) regarding exposure to the project. Both sections however focused on communication with teams, changes to clinical practice and impacts. While it is accepted that data obtained from focus groups is influenced by group dynamics and consensus, data sources from different qualitative methodological approaches can be blended and contrasted, provided they are at first analysed thematically in a separate manner. An overarching thematic pattern-matching can be achieved to come to an explanation of the data, which is the method used here. [168]

The analytical approach taken was Flick's content analysis,[169] whereby themes and subthemes were categorised within a pre-existing template (within the instrumentation). With this approach however care is taken not to artificially represent data within the template but to introduce new themes when identified.

This approach required peer review to ensure analytical trustworthiness, which was conducted within the research team. The analysis from the focus group concentrated on the identification of best methods for delivering the alerts and recommendations in order to inform the AKI and AKI risk alert system development and implementation. The aim was for this qualitative analysis to be part of a larger longitudinal qualitative research design, with two further focus group waves with implementation of the AKI risk alerting within the clinical decision support system. Longitudinal qualitative research (LQR) involves repeat interviews or observations of, ideally, the same research subjects over time. [170] In recent years, LQR has been used in a number of health-related areas to generate rich data and a deeper understanding regarding people's perspectives and experiences and how and why these may change over time in order to improve practice. [171-174] Rather than comparing findings at a number of distinct moments, LQR is concerned with the comparison of different, continuous processes of change. The benefits of the longitudinal design will be that it will permit the same participants to be involved in identifying practice challenges and solutions, in developing methods for how alerts and recommendations can be best delivered for action, and for examining and reflecting on the effects with regard to practice change as well as system evaluation and improvement. The qualitative aspect of both this and the further study will strengthen the production of potentially transferable practice guidelines and system accessibility across the NHS.

Results

The data analysis here was performed by Professor Jenny Billings (Professor of Applied Health Research, University of Kent), with advice and data review by Dr Michael Bedford. The full results including quotations, of the qualitative analysis of the use of the SAKI AKI alert system by the critical care outreach nurses and the renal consultants are documented in Appendix 6.

In summary, there was a desire by participants to support their colleagues in the management of these often complex patients, and an understanding of the potential benefit of use of the system in the management of these patients. At the time of study, the SAKI AKI alert system had been in use by the critical care outreach nurses and renal consultants for a period of two years, and therefore with the use of the present tense in describing their views on the impact of the system, their views appeared to be enduring.

One important outcome from this study was the uncertainty of roles. It became very apparent that while both the critical care outreach nurses and the renal consultants saw their role as firstly alerting the medical teams to the fact that their patient had AKI, and then to provide clinical assessment and advice (critical care outreach nurse), or advice over the phone (renal consultant), that both groups were then worried as to when their responsibility for the patient ended. Particularly for the critical care outreach nurses there was the worry that, especially on surgical wards, they were believed to have taken over responsibility for the clinical management of AKI from that point on. They also found it harder to communicate the alert to the surgical and orthopaedic teams, and also reported a lack of recognition of AKI and how to manage these patients by these teams. They also experienced a lack of understanding by the clinical teams as to why they were being contacted. In terms of follow-up of cases, the majority of the consultants interviewed did not follow-up cases and some felt strongly that their role was to provide the initial alert only with the responsibility then being with the clinical team looking after the patient. For the outreach nurses there was a variance in follow-up, both related to the fact they had reviewed the patient in person on the ward and written in the notes giving them a feeling of responsibility, and also that a number of the patients with AKI may need follow-up by the outreach team as they are generally unwell and not directly related to AKI. For the consultants there was also the concern that the advice they gave over the telephone was not documented in the clinical notes.

In terms of user-friendliness of the system there were issued raised with regard to slow navigation, the need to access other IT systems to understand the context of the patient, and fitting the use of the system into their workload.

One issue that raised both advantages and disadvantages was the fact that the data on the AKI report documented patients with AKI from the previous day. In terms of allocation of workload, it was clear that this was much easier to manage, as in it was possible to print a list of patients requiring review at the beginning of the day, and then systematically review all of those patients. However, in terms of a disadvantage of this approach, the clinical intervention was being instigated a day after the diagnosis of acute kidney injury (AKI) was evident from blood testing and so delaying the clinical intervention and possible benefits in outcomes.

Communication with and contacting the clinical teams looking after the patients with AKI was also a significant problem, more so for the renal consultants who were often not based at the site of the patient and so used bleeping of junior doctors to make contact, and less so for the critical care outreach nurses who physically reviewed the patient on the ward. This took a significant amount of time. For the renal consultants, strategies such as calling the ward and speaking to the nursing staff looking after the patient had been developed to overcome this problem. In the most part, when contact was made with the clinical teams, most users found that they were already aware of the presence of AKI in their patient.

The critical care outreach nurses thought that the AKI stickers as described above, (placed by them in the medical notes of the patients at the time of review) when placed in the medical notes were successful in developing awareness of acute kidney injury.

In terms of the benefit of using this alert system to aid in the management of AKI, the critical care outreach nurses generally saw the preventive benefits in terms of clinical management, and also the educational benefits by teaching the clinical

teams looking after the patients, developing the concept of education at the point of care. However, a number of users did not see these benefits, importantly the renal consultants who in the most part found that the clinical teams when contacted were already aware of the AKI and had instigated management changes in response to this. This could however, after two years of the alerting system, and clinician education sessions, be a result of a better understanding generally now of the importance of efficient recognition and effective management of acute kidney injury.

When asked about the future of the alerting system and possible improvements, users suggested increasing the speed and usability of the system, and delivering up-to-date clinical information. Another important improvement requested was to provide an easier method of contacting and communicating with the clinical team looking after the patient, and along with this ensuring that the clinical responsibility remains with the clinical team with specialist advice from the critical care outreach nurses or renal consultants.

Conclusions

In conclusion, while the SAKI AKI alert system had significant benefits in terms of clinical intervention in acute kidney injury, and importantly the concept of education at the point of care, this study highlighted a number of key areas requiring improvement. The key areas highlighted in the qualitative analysis included real-time delivery of AKI alerts, clear responsibility of care to be with the clinical teams with advice from the critical care outreach nurses and renal consultants as required, and improved communication with the clinical teams looking after the patients. From a user experience point of view of the system, users required improvements in ease of use and accessibility of the system.

Alerting in real time to the point of care

With the above qualitative study in mind the next step, (in parallel with the development of risk modelling to determine patients at risk of developing AKI that can then be alerted alongside the patients who already have AKI), was to

improve the usability and functionality of the alerting system to deliver these alerts to the point of care. In clinical medicine communication often has a key role in medical errors, and also is of key importance when trying to improve clinical management procedures. With communication as the focus of improvements of the alerting system, a development partnership was entered into with a commercial company (Doctor Communications Limited later changing their name to Careflow Connect Limited) whose key aim was to bring social media technology securely into healthcare to improve clinical communication. The aim was to deliver real-time alerting to clinicians at the point of care, and allow collaboration within the clinical team also involving the specialist renal team and critical care outreach teams.

This new system is named Careflow. Careflow holds information securely in the cloud and so is accessible with an internet connection, both on standard desktop computers and also on mobile devices. The data is encrypted at rest and in transit, and no data is stored on the devices on which it is viewed, maintaining data security and complying with strict NHS information governance. This mobile technology allows clinicians to access patient data and receive clinical alerts about their patients in real time to the point of care, and the social technology allows them to discuss and collaborate around the patients and clinical alerts in real-time.

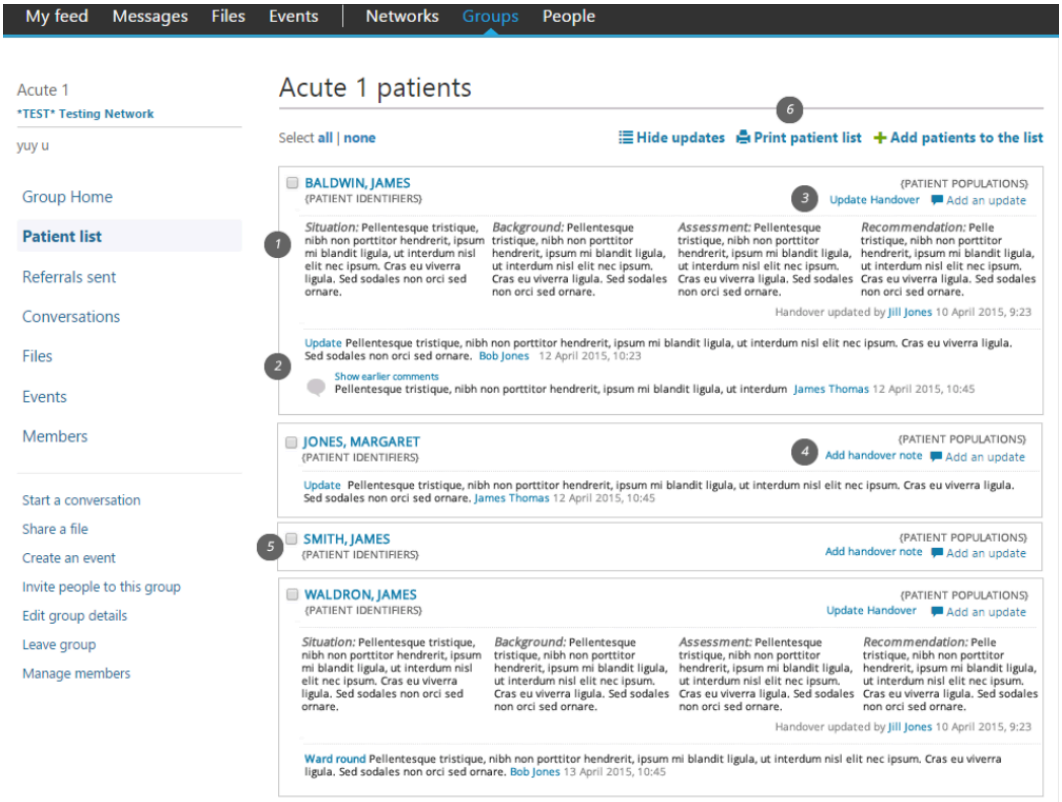
In order to address the issues of both ensuring that the message of the AKI alert was delivered to the clinical team looking after the patient, and that they retained clinical responsibility for the patient and the management of the acute kidney injury (as suggested by the qualitative analysis), there needed to be a realigning of the alert delivery strategy. The old static system of AKI alerting / reporting as described above, involved alerts being delivered via an intranet portal to the renal consultants and critical care outreach nurses, and then this information being conveyed to the clinical teams looking after the patients, with the addition of advice and guidance on management. The aim of the new alerting system was to reverse this by delivering the AKI alerts directly to the clinical teams at the point of care, but also to the specialist renal and critical care

outreach teams at the same time to allow collaboration and advice in real time. This therefore required the clinical teams to take ownership for their patients that they would then receive alerts for. While it is possible to determine from the hospital electronic patient administration system (PAS) which consultant is responsible for a given patient's care, and from this try and determine the junior doctors to deliver the clinical alerts to, this is often not successful or robust for a number of reasons. In the initial 24 to 48 hours of a patient's admission to hospital (often when acute kidney injury may become apparent) the consultant responsible for the care of the patient may change a number of times; from the on-call consultant to a consultant working in a medical assessment unit, to then a consultant on a medical ward. This may not be accurately updated in a timely manner on the PAS, leading to uncertainty in alert delivery. Also in terms of the junior doctors in the clinical teams both the on-call teams and the teams on the wards are variable (due to on-call rotas, leave etc.) and it is difficult to define at a given point in time which doctors are responsible for which patients. This therefore posed the first problem in the reversal of the alert delivery strategy, but was also the core of the problem experienced with the SAKI AKI alert system, of the renal consultants being unable to find and communicate with the clinical teams looking after the patient with AKI. The answer to this was to find a role that the clinical teams looking after a patient perform which identifies that they are responsible for that patient and then using this as the basis for the alerting and communication system. This was the patient list.

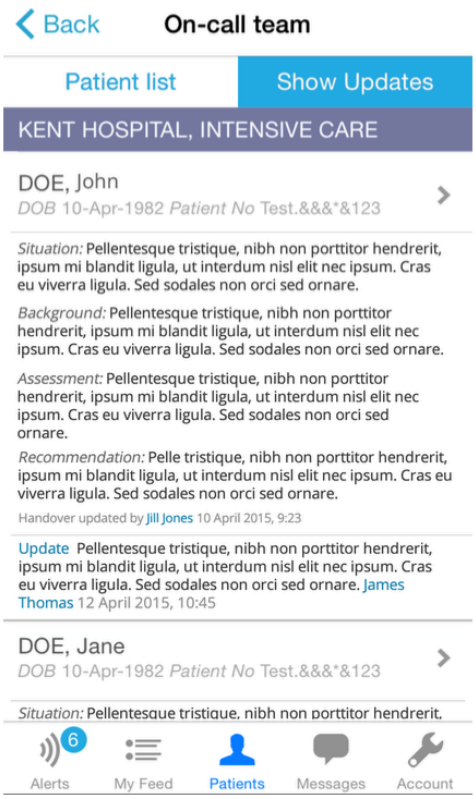
What is common to both a doctor and nursing handover is the 'handover list' or 'patient list'. In general, (although variable between teams) this list documents each of the patients under the care of a given team, their demographics, hospital and NHS number, past medical history, reason for admission, results and investigations so far, and the medical plan for the patient's care. These lists are often created on a word processing document or spreadsheet, and stored on a single computer desktop. They are often printed at the beginning of the day, annotated during the day as the patients care progresses, and then the document updated on the computer at the end of the day. These summary sheets can easily be misleading, misinterpreted or lost (a significant information governance and

data protection risk) and then key clinical information is not transferred to the clinical record and results in no action being taken. In terms of patient specific information being held on these 'patient lists' it is also vital that confidentiality is maintained. The terminology and clarity used in these lists is also often very different to how a healthcare professional would document within the clinical notes and patient record. Within the NHS there is a legal requirement that all clinical information is recorded in clinical notes as part of formal information governance procedures. Yet the recording of some patient information in everyday clinical practice remains outside the domain of 'formal' and takes the form of more 'informal' recording, manifested through the documentation of information within these so-called 'handover lists' or 'patient lists' for shift changes. This therefore proved an opportunity to both formalise these 'patient lists' to comply with information governance and data security, but also provide a clear record of which clinical teams and importantly junior doctors were responsible for a given patient to allow AKI alerting to the clinical teams at the point of care. This is also the case for other clinical alerts as will be discussed later.

A clinical list functionality (Figure 24) was therefore developed within Careflow to replicate the 'handover list' or 'patient list' used by the clinical teams, using the Situation Background Assessment Response / Recommendations (SBAR) format to document patient information. This provided the benefits of standardisation of practice across the organisation, transparency and audit of data (all data entry is recorded with the user details and the date and time of the entry), data security, the ability of other members of the team to see updates to the list in real-time, viewing of the list on any desktop computer or mobile device, and importantly the definition of a clinical team responsible for a given patient.



(a)



(b)

Figure 24: The 'patient list' in SBAR format on Careflow – (a) on the website, (b) on the Careflow mobile app.

With the definition of the clinical team responsible for a given patient, the AKI alert could then be developed. The clinical team would automatically be subscribed to the AKI alerts for their patients. The AKI alerts would be sent to and received by the clinical teams in real-time as soon as the information (in the form of a creatinine blood test result defining acute kidney injury) was available. In this way mobile IT technology is being used to create a shift change in healthcare delivery.

Traditionally information flow in healthcare involves sequential processing (Figure 25). For example, blood testing for patients is often ordered the night before. The phlebotomists take the blood samples the next morning. The results of these blood tests may be available mid-morning, however they are often not checked by the clinical teams until later in the afternoon as the morning is taken up with the ward round of the patients and then the early afternoon with carrying out clinical jobs created from the ward round. Therefore, it may be late in the day that the blood test results are checked and there is recognition of the acute kidney injury for a patient. This also assumes that prior to the introduction of AKI reporting the clinical team appreciated that a creatinine result in the context of that patient defined acute kidney injury.

This new technology changes the traditional sequential (Figure 25) processing of information to conditional (Figure 26) processing, whereby the moment a result signifying acute kidney injury is available it is delivered instantly to the point of care in real-time to the clinical team looking after the patient, and the management of the patient can then be changed, reducing treatment delay.

AKI alerts were developed with a separate alert for each stage of acute kidney injury (Figure 27). The alerts are received in real-time to users' mobile devices and stored in a feed in chronological order (Figure 27). If the user puts themself 'on duty' (Figure 27), an additional push notification is sent to their mobile device each time an alert is received, in order to ensure they are aware of the new alert.

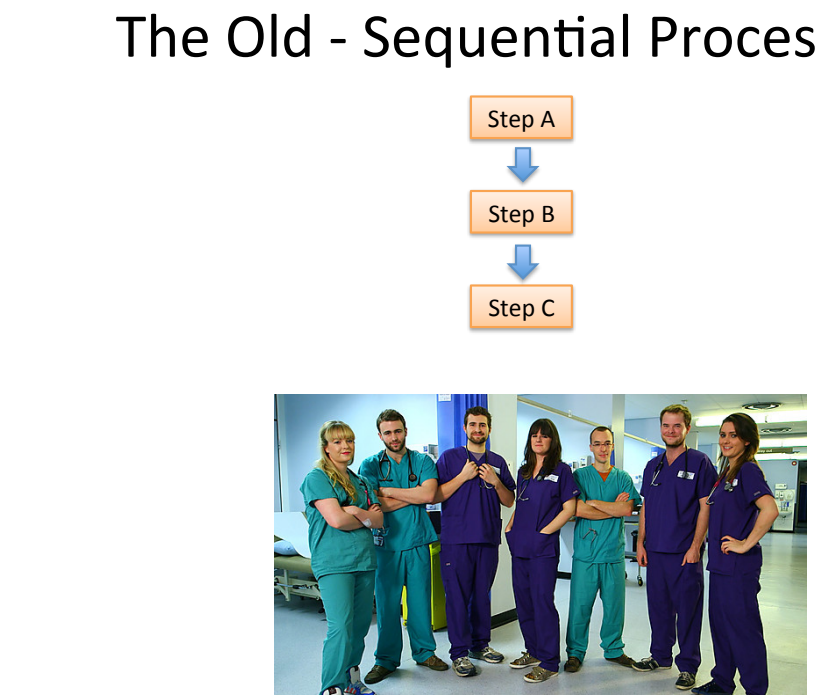


Figure 25: The sequential processing of traditional medicine, following a routine of data delivery and information receipt.

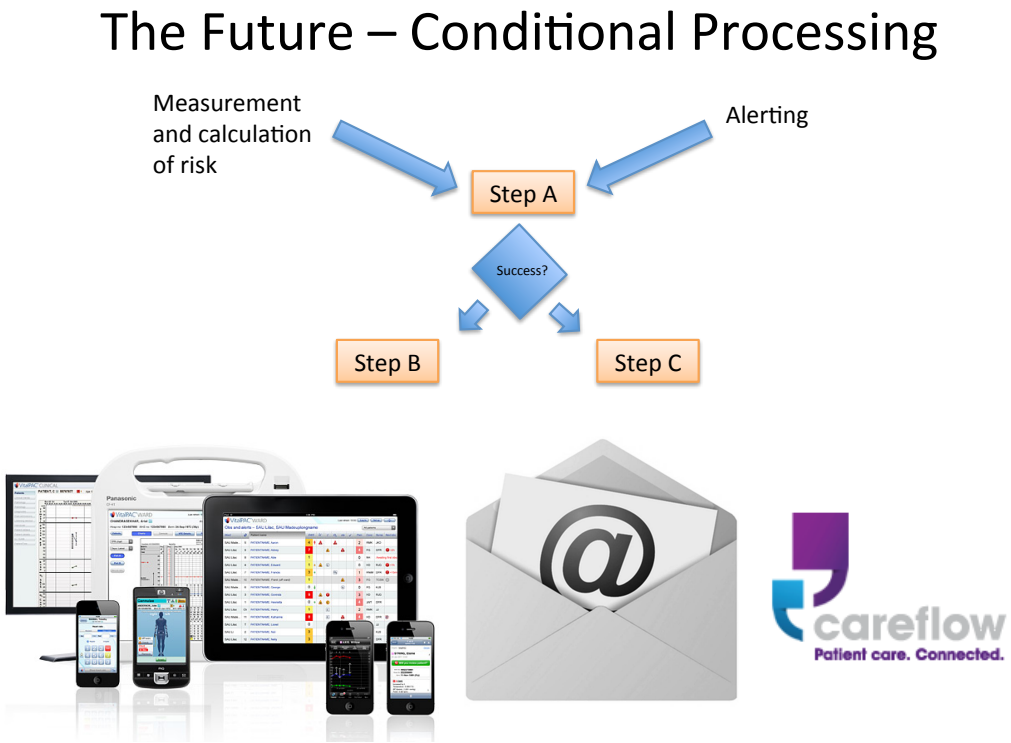


Figure 26: The conditional processing enabled through technology of the delivery of information to the right person in real-time.

The alerts included the details (Figure 28):

- patient demographics
- patient location
- consultant responsible for the patient
- creatinine result triggering AKI
- baseline creatinine result
- list of previous creatinine results over the past 1 year
- a link to local and national guidelines for AKI
- contact details for the specialist renal team for further advice
- a link to open the pathology system in the context of the patient in order to review other blood test results for that patient

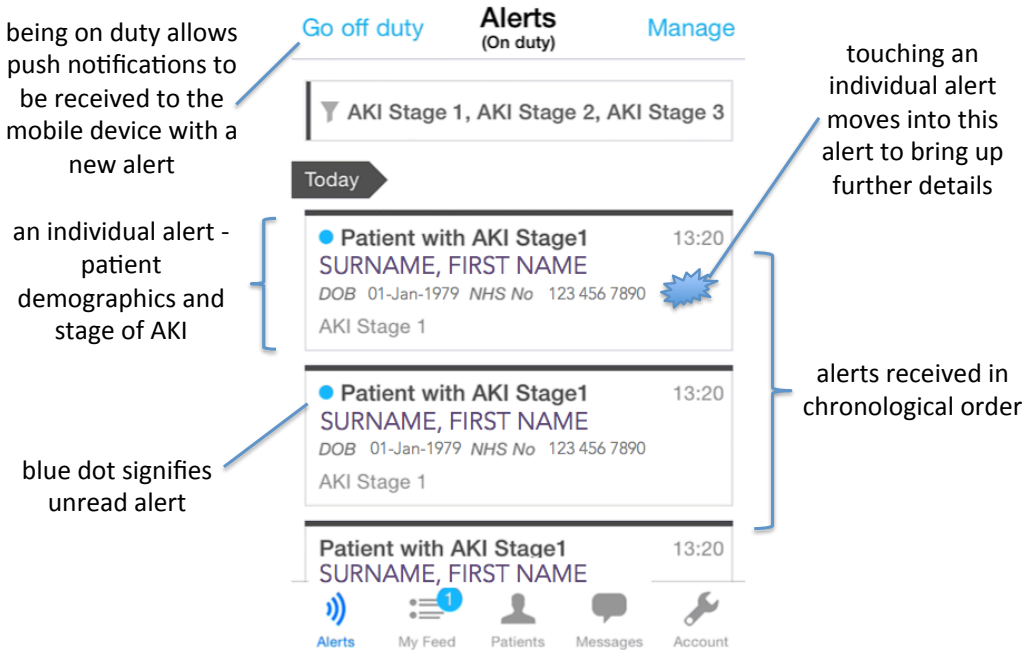
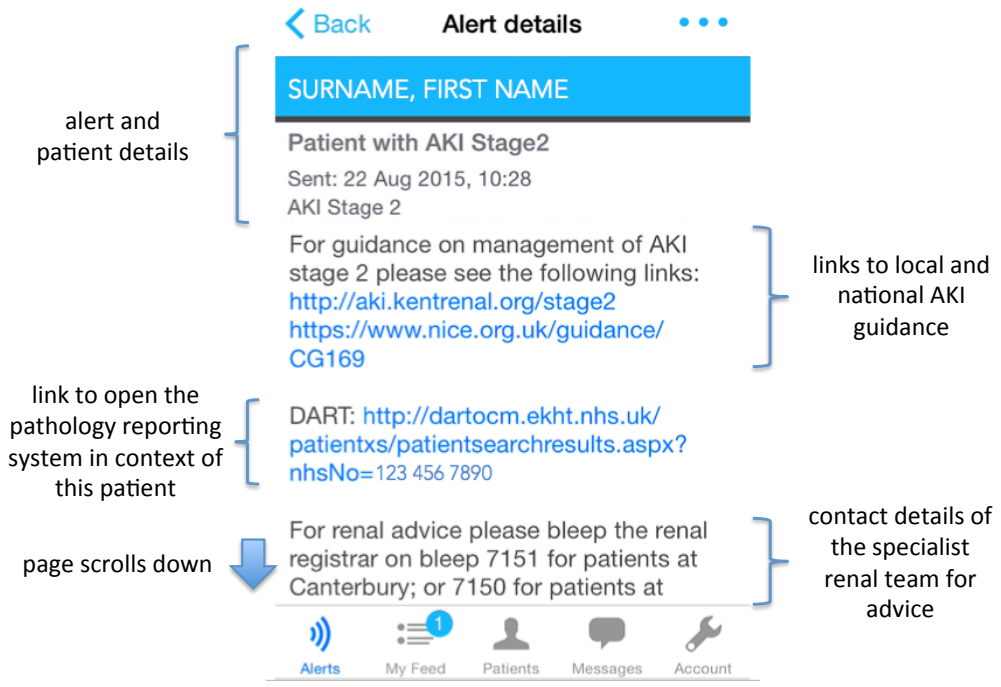


Figure 27: The AKI alert feed on a mobile device, listing the AKI alerts in chronological order.

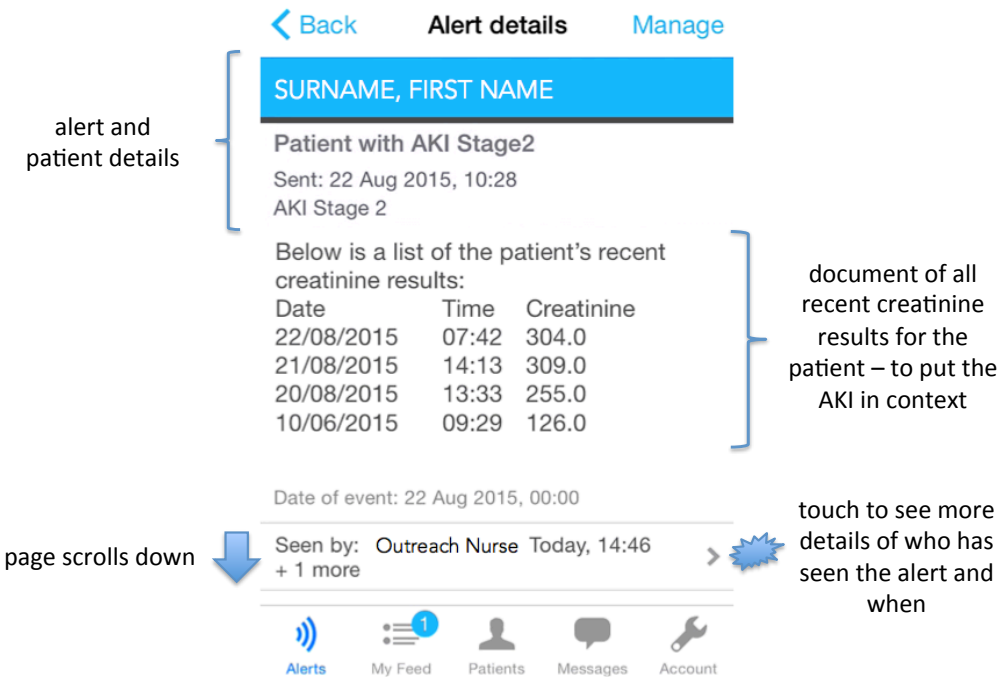
Clicking on an alert brings up further details for the alert, as shown in Figure 28.


Back
Alert details
patient demographics banner
SURNAME, FIRST NAME
DOB 01-Jan-1979
NHS No 123 456 7890
Gender Female
date, time and stage of AKI alert
Patient with AKI Stage2
Sent: 22 Aug 2015, 10:28
AKI Stage 2
Consultant:
Ward:
Hospital:
patient location and consultant responsible for patient's care
creatinine result triggering AKI alert, and baseline creatinine
Result: 304.0 22/08/2015 07:42
Baseline creatinine: 126.0
For guidance on management of AKI stage 2 please see the following links:
page scrolls down
Alerts
My Feed
Patients
Messages
Account

(a)


Back
Alert details
alert and patient details
SURNAME, FIRST NAME
Patient with AKI Stage2
Sent: 22 Aug 2015, 10:28
AKI Stage 2
For guidance on management of AKI stage 2 please see the following links:
http://aki.kentrenal.org/stage2
https://www.nice.org.uk/guidance/CG169
links to local and national AKI guidance
link to open the pathology reporting system in context of this patient
DART: http://dartocm.ekht.nhs.uk/patientxs/patientsearchresults.aspx?nhsNo=123 456 7890
page scrolls down
For renal advice please bleep the renal registrar on bleep 7151 for patients at Canterbury; or 7150 for patients at
contact details of the specialist renal team for advice
Alerts
My Feed
Patients
Messages
Account

(b)



(c)

Figure 28: The details in an AKI alert. Further information is viewed in the alert by scrolling down the screen (a to c).

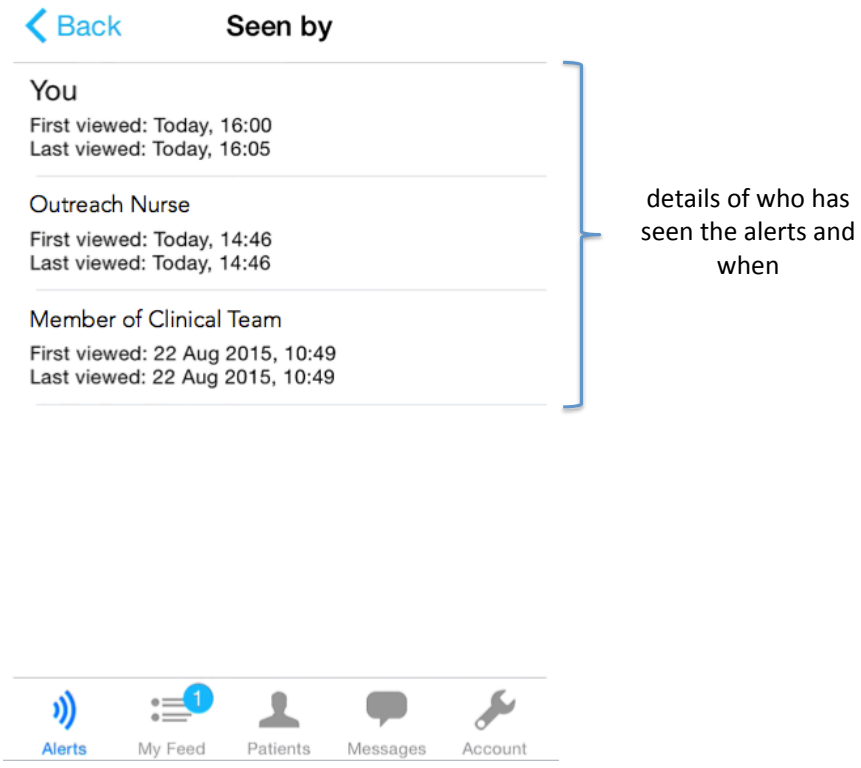
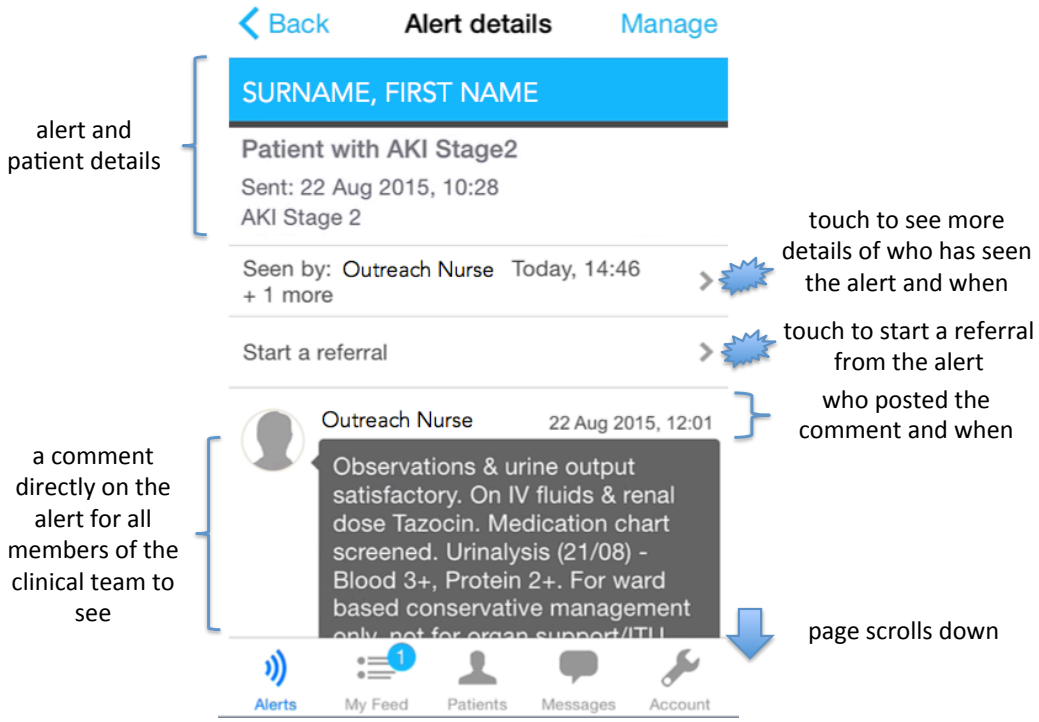
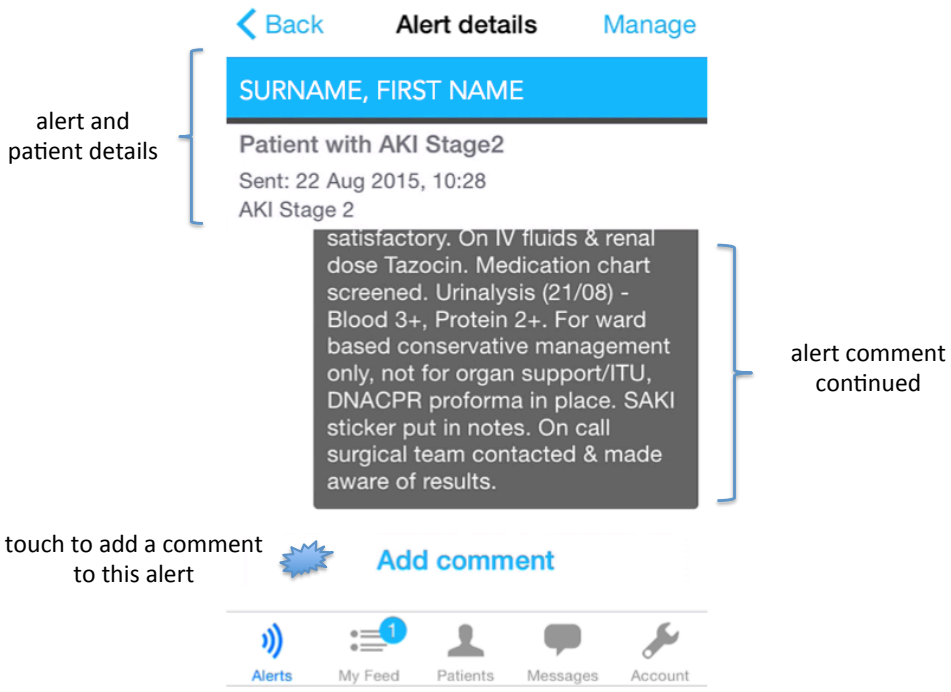


Figure 29: AKI alert audit trace: the screen showing who has seen the alert, and when.

Importantly the additional unique functionality of the clinical alerts (in this case AKI alerts) within the Careflow system is the record of and ability to see when other members of the clinical team have seen the alert (Figure 28 and 29), and the ability to comment directly on and socialise an alert so that the comment can then be seen instantly by the rest of the clinical team (Figure 30). This ensures real-time collaboration within the clinical team. The system also has the ability to start referrals in an SBAR format (Figure 31) directly from the alert, to for example the renal or critical care outreach teams.



(a)



(b)

Figure 30: Real-time collaboration.

Comments made directly on the alert for all members of the team to see. Further text of the comment, and the ability to add another comment to the alert, are seen by scrolling down the alert ((a) to (b)).

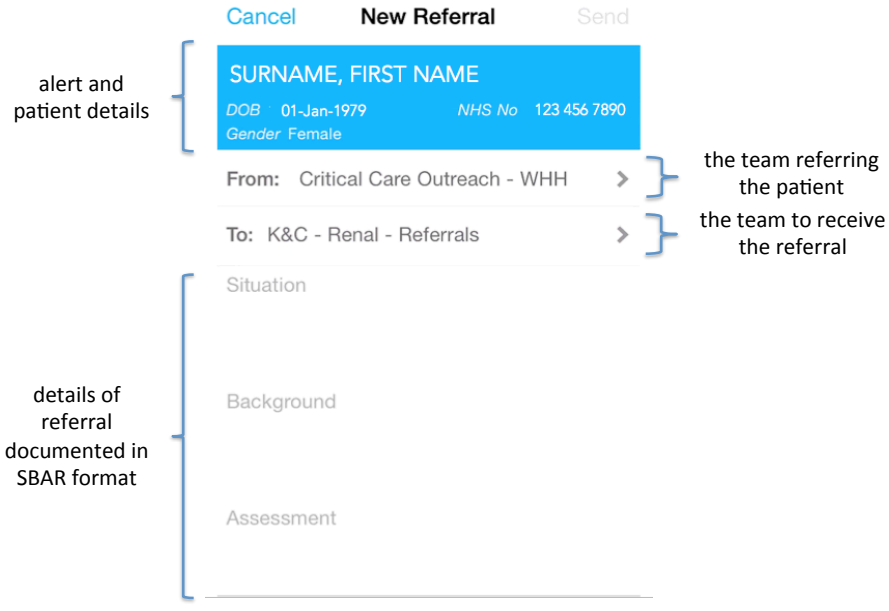


Figure 31: Referrals in SBAR (Situation, Background, Assessment, Response / Recommendations) format, started directly from an alert.

Conclusion

The functionality developed and delivered in the Careflow alert system addresses the feedback in the qualitative analysis, from the use of the previous alerting system (delivered via Qlikview, Qlik.com) used for acute kidney injury at EKHUFT. The system provides real-time acute kidney injury alerts to the point of care, delivered to the clinical teams looking after the patients on their mobile devices, accessible anywhere. This re-aligns the clinical responsibility for acting upon the alert, ensuring this responsibility is with the clinical team responsible for the patient. It also ensures clinical transparency with the ability to see when an alert was viewed and by whom in the clinical team. It also enables clinical comments to be placed directly on the alert to allow collaboration within the clinical team in real-time as all members of the clinical team can see these comments as soon as they are entered onto the system. This does not however remove the specialist renal and critical care outreach teams from the clinical collaboration as they can also view the alerts and see who from the clinical team has seen the alerts and also view and if necessary add to the clinical comments on the alerts. This allows the specialist teams to collaborate with the clinical team looking after the patient, and give advice and support as and when required. If the clinical team wishes to actively ask for advice and support, then the referral functionality can be employed. This setup removes the communication challenges reported in the qualitative analysis, and ensures that the patient receives specialist intervention as early as possible, whether this is referral to the critical care outreach team, referral to the intensive therapy unit (ITU) / team, or discussion with the specialist renal team.

The Careflow system to deliver patient lists, acute kidney injury alerting and electronic referrals was initially implemented with the critical care outreach teams on all three sites at EKHUFT and the renal team. Following this the system was rolled out across the organisation to all medical and surgical teams.

A hyperkalaemia alert was also developed within the Careflow alerting system in order to ensure timely management of this complication of acute kidney injury, which from the NCEPOD report [100] we know is not often achieved.

With an improved system in place, based on user level feedback, to provide real-time alerting of patients with acute kidney injury to the point of care, this satisfies the third aim of this thesis.

Chapter Summary

The work reported here has developed a simple reporting / alerting tool to define all patients within a hospital trust who have acute kidney injury (AKI), to allow focused and standardised clinical intervention by Critical Care Outreach Nurses and specialist Renal Consultants. Importantly the use of Critical Care Outreach Nurses to support the management of AKI has been replicated in numerous other NHS trusts throughout England following this work, and is currently being tested in a project supported by the National Institute for Health Research (NIHR).

Using qualitative methodology the integration of the alerting system into clinical care was assessed, in particular the effect of professional interactions, information sharing, and personal and professional characteristics on the use of electronic clinical information and clinical decision support. The study concluded that while the alert system had significant benefits in terms of clinical intervention in AKI, and also the realisation of unexpected benefits such as the concept of education at the point of care, the study recognised a number of key areas that required improvement. The key outcomes from the qualitative analysis included the need for real-time delivery of alerts to the point of care, clear responsibility of care to be with the clinical teams with advice from Critical Care Outreach Nurses and Renal Consultants, collaborating in real-time with improved communication. This work has informed further developments in alerting reported here and future work as electronic alerting and real-time communication to the point of care with the utilisation of mobile device technology becomes more widespread within the health service.

The second stage of the work in this chapter, as part of a development partnership with a commercial company, developed a new alert system to provide real-time alerting of patients with AKI to the point of care, utilising mobile device technology, and allowing collaboration with specialist teams in real-time. This successful system has now been implemented in a number of NHS trusts in England to provide AKI alerting as well as other patient safety alerts and for clinical communication and collaboration in real-time. Since this development a number of other companies have created similar systems including Google Deepmind.

With now an improved method of providing real-time alerting of patients with AKI to the point of care, this will allow early intervention and management changes to improve outcomes. These improvements need to be further assessed in a formal clinical trial.

With these improvements in management of AKI, the next stage in the quality improvement process is to move further back in the disease process to before acute kidney injury develops and aim at preventing AKI by determining risk. The first step in determining this risk is to identify key risk factors and their association with acute kidney injury.

Chapter 4: Risk of AKI

Aim

The aim of this chapter is to explore potential risk factors for acute kidney injury (AKI).

Introduction

In any disease process, while we can optimise our measures in place (as above) to alert to the presence of a disease (in this case acute kidney injury (AKI)) and manage it effectively and efficiently at recognition, the ultimate form of treatment is the prevention of the disease occurring in the first place. In order to prevent AKI, we must have a clear understanding of what factors convey a risk of AKI to the patient, and in what situations. This also then highlights time points in the clinical pathway when risk assessment should be carried out and clinical intervention informed / directed.

As described, the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the setting of AKI, highlighted systematic failings in identification and subsequent management. [100] One of the reports key recommendations was that risk assessment for AKI should be carried out for all emergency admissions. Following on from this report, the 2010 NCEPOD report 'An Age Old Problem; A review of the care received by elderly patients undergoing surgery' suggested that "Risk assessment [for surgery] must take into account all information strands, including risk factors for acute kidney injury."[176] The report also suggested "a need for continuous post graduate education of physicians, surgeons and anaesthetists around the assessment of risk factors for the development of AKI in elderly surgical patients." [176]

However, a number of patients present to hospital who already have AKI. From the epidemiological data presented in Chapter 2, 73.6% of patients with AKI in hospital had AKI already present at the point of admission. In these patients we

can assess their risk of AKI as they enter the emergency department to ensure that patients at high risk have their kidney function checked, to reveal their underlying AKI. In patients who have established AKI, the risk assessment should not stop there, we can then risk assess to determine which patients are at high risk of experiencing worsening AKI and hence are likely to require specialist or critical care intervention.

Following the determination of which risk factors are important in the development of AKI, or of worsening AKI, as there are a large number of factors involved, these can then be employed in risk models and risk scores to determine the individual risk of a patient, and thereby more accurately guide clinical management. To date, the development of risk models in AKI has mainly focused on the clinical areas of cardiac surgery and radiology contrast scans, in which there is a more predictable exposure to risk.

In the disease process of acute kidney injury, a patient experiences an event (Figure 32). This event may be an illness for example a chest infection, urinary tract infection, or myocardial infarction, which carry a risk of AKI. This event could also be an iatrogenic risk, for example a radiological scan involving the infusion of intravenous contrast, which again carries the risk of AKI. Once there has been a harm to the kidneys, and the patient has a defined AKI, there is then the risk of worsening AKI and of resultant sequelae, for example hyperkalaemia, fluid overload, the need for renal replacement therapy, and the resultant morbidity and mortality. In the disease process there are therefore two points (Figure 32) at which we can intervene. When the patient experiences an event which carries a risk of AKI we can intervene in order to prevent the development of AKI, and when the patient already has AKI we can intervene in order to reduce the resultant sequelae of AKI and prevent worsening AKI.

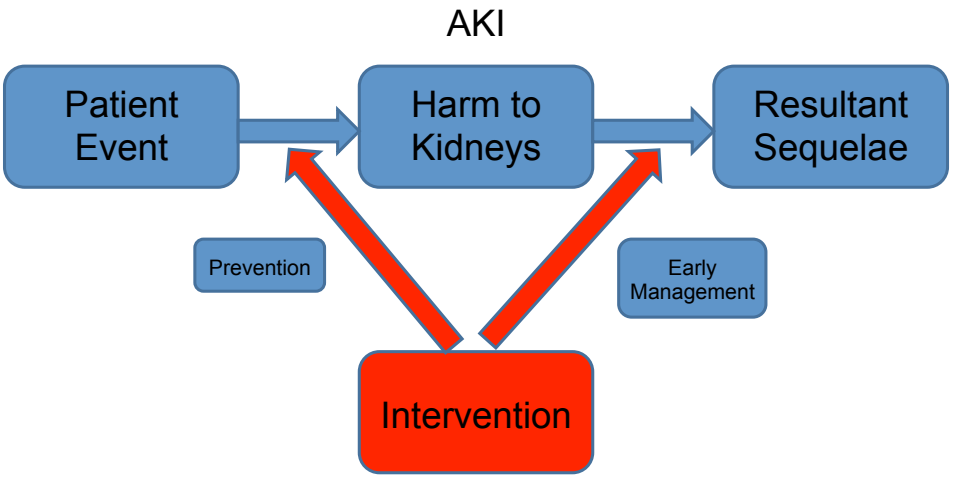


Figure 32: Points of clinical intervention in the disease process of acute kidney injury (AKI).

At these points of clinical intervention, we can then provide an assessment of risk factors in order to guide clinical intervention and provide management changes in high-risk patients.

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury published in March 2012,[83] suggests that risk assessment should be carried out at 4 points:

1. Before exposure to an insult
2. After exposure to an insult
3. Upon development of AKI
4. After recovery from AKI

Before exposure to an insult

In clinical medicine there are certain procedures or treatments that a patient may experience as part of their clinical management that are essential in their care, but carry an inherent risk of precipitating AKI. Some insults may not be avoidable and in these cases the patient's care can be optimized to reduce the risk of AKI. In some cases, when the risk of AKI is fully appreciated, this risk may

outweigh the benefit of the procedure or treatment. In other cases, while the benefit of a procedure or treatment may outweigh the risk, modifications in dosing or exposure may reduce the risk of AKI, as may modifications in current medications (for example diuretic treatment) and optimisation of fluid balance / hydration of the patient.

Risk assessing the patient in the context of the expected exposure to the insult can allow appropriate decisions then to be made regarding the risk benefit of the procedure or treatment, modifications in dosing and exposure, and clinical optimization prior to the procedure.

After exposure to an insult

After a patient is exposed to an insult, whether this is iatrogenic or the presenting disease of the patient, as it takes up to 48 hours for the creatinine to rise in acute kidney injury, the AKI may not be immediately apparent. In this case we can then predict which patients are at risk of developing AKI from the insult they have sustained. In these patients we can provide clinical intervention, both to make management changes (Table 8) to aid prevention of AKI following the insult, and also to ensure repeat kidney function checks to monitor for the development of AKI.

Table 8: Clinical interventions in the management of AKI

Regularly assess fluid status
Reverse hypovolaemia / hypotension
Stop and avoid nephrotoxic agents (ACE inhibitors, ARBs, NSAIDs)
Assess drug dosages with respect to level of kidney function
Look for and treat infection early
Recognise and treat hypoxia
Check for acidosis
Urinalysis
Renal tract ultrasound
Daily kidney function

Upon development of AKI

When we know a patient has AKI, as evidenced from blood testing, this is not the end of the story. At this point we have the opportunity to intervene early at recognition to make management changes (often the same as prior to the development of AKI (Table 8)), to effectively manage the AKI and both prevent worsening of AKI and the development of sequelae including the significant morbidity and mortality demonstrated in Chapter 2.

By risk assessing patients at this point and defining patients at high risk of worsening AKI or resultant morbidity and mortality, we can focus clinical and specialist care to these patients.

After recovery from AKI

As described in Chapter 1 there is a complex interplay between AKI and CKD. Following an episode of acute kidney injury, a patient may have complete recovery of their kidney function, this recovery may not be complete, resulting in new chronic kidney disease (CKD), or the progression of pre-existing CKD. Patients who have experienced an episode of AKI may also be at increased risk of morbidity including cardiovascular disease, and mortality in the future.

In this case risk modelling may be important to highlight patients that following an episode of AKI require follow up to diagnose or manage resultant CKD, and other resultant morbidity.

Defining Risk in Clinical Practice

If a patient's risk of AKI, or of worsening AKI if already present, can be defined, then clinicians can be alerted to these 'at risk' patients and management changes and interventions can be instigated early in order to prevent or at least reduce the risk of the patient developing AKI, or of experiencing worsening AKI if AKI is already present.

In any disease process the ultimate treatment is prevention. In the disease process of AKI risk factors include pre-existing co-morbid disease, the presenting illness, and also the treatment given for this illness. From these risk factors we can attempt to define a patient's risk.

Risk Factors

Irrespective of the point of determination of risk (before or after exposure to an insult, upon development or after recovery from AKI) there are a number of risk factors that are common ('generic') to all settings. [177-179] One of the most important and indeed modifiable risk factors for AKI is in regard to volume status and in particular volume depletion with often resultant hypotension which leads to the development of pre-renal AKI, the most common form of AKI. Regular assessment of fluid status and reversal of hypovolaemia / hypotension are therefore the most important clinical interventions (Table 8) in a patient at risk of or with acute kidney injury.

In the majority of disease processes older age is found to be a risk factor. This may be related to the increasing co-morbidity burden (either overt or as yet unknown) with advancing age, or in relation to vascular changes with age described in Chapter 1. In most cases, irrespective of the insult precipitating AKI, there is evidence that with increasing age there is an increasing risk of both community-acquired and hospital-acquired AKI. [70,180-184]

As with other disease processes there is a reported gender discordance in AKI, however unlike with most chronic kidney diseases, in AKI a female gender has a higher risk for AKI, which has been confirmed in a number of causes of AKI. [180,182,183,185]

As would be expected and as already eluded to, co-morbidity either collectively (in terms of co-morbidity scores) or individually, are a significant risk factor for AKI. Firstly, chronic kidney disease (CKD) is an important risk factor for AKI [180-183,186-192] as already described in Chapter 1. However as suggested in Chapter 1 there still remains a debate as to whether patients without CKD may have less

severe AKI (often silent and discrete episodes in the community), which may not be captured in epidemiological studies, suggesting an increased incidence of AKI in CKD. The 'intact nephron' hypothesis [20,21] also contradicts the increased risk of AKI in CKD. At present however the epidemiological data available suggests a significantly higher risk of AKI in patients with CKD, in both community or hospital-acquired AKI. [180-183,186-192]

Another risk factor, again in relation to vascular disease is cardiac disease, and this increased risk of AKI is commonly reported with cardiac intervention either percutaneous or surgical for ischaemic or valvular cardiac disease. [183,185,192-199] Poor cardiac function, quantified by a reduced left ventricular ejection fraction is also described as being a risk factor for AKI, notably for cardiac surgery [183] or in relation to contrast nephropathy. [200]

Diabetes is also another commonly described risk factor for AKI, particularly in patients with pre-existing CKD. [201] Again diabetes is associated with an increased risk for both community and hospital-acquired AKI. [70,181]

Other co-morbidity including; chronic lung disease, [183] chronic liver disease, [182,190] myeloma, [202,203] and malignant disease in general. [204]

In terms of pathology results (blood testing and microbiology) there has been little description in the literature of these results and their association with risk of developing AKI. Of note one study has shown that a low serum albumin level is associated with an increased risk of AKI, and also an increased risk of mortality in those who develop AKI. [205] The work in this thesis (Chapter 5) aims to explore further the use of available pathology results to predict risk of AKI.

A further consideration in defining a patient's risk of AKI is medication burden at the time of exposure to another risk factor for AKI (for example operative intervention, contrast administration, presenting disease process such as sepsis). An increased medication burden may increase susceptibility to AKI in these situations, but may also be simply a reflection of underlying co-morbidity. In

relation to renin-angiotensin system blockade as a risk factor for AKI there is conflicting evidence with studies reporting differing outcomes. [206-209] In preparation for work in Chapter 5 of this thesis a study was performed to assess the effect of treatment with renin-angiotensin system (RAS) blockade in primary care, on the incidence of AKI, (see Appendix 4: Paper 4: 'Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care?'). [210] This study demonstrated that the use of RAS antagonists increased the risk of AKI in general, independent of common confounding variables, however after correction for confounders the risk fell away and became non-significant for moderate and severe AKI. [210] The relationships between medication burden and risk of AKI will be assessed further in the risk modelling in Chapter 5.

In terms of risk of AKI, and in particular the development of models / scores to define a patient's risk, in the literature the majority of the reports focus on the need for renal replacement therapy (RRT) after cardiac surgery. One of the first of these was by Chertow *et al* who produced a risk model for predicting AKI after cardiac surgery, based on a population of 40,000 patients from 43 Veterans Administration Hospitals in Virginia who underwent cardiac bypass or valvular surgery. [211] From this study the described interactions between risk factors for AKI were used to develop a risk stratification algorithm. [211] Despite its widespread use this study did however have a number of key limitations, importantly the population was predominantly male and lacked African-American patients.

Thakar *et al* produced a clinical risk score to predict AKI requiring RRT following cardiac surgery, based on 33,217 patients from the Cleveland Clinic who had cardiac surgery between the years 1993 and 2002. This clinical risk score (Table 9) included 13 pre-operative risk factors. Each one was weighted with a defined number of points (Table 9). [183] By summation of these points, a risk score (0 to 17) was determined for each patient. A score of 0-2 was defined as low risk, with a 0.4% chance of developing AKI requiring RRT. A score of 9-13 was defined as high risk with a 21.5% chance of developing AKI requiring RRT. [183]

Table 9: Risk factors for AKI and weightings (Thakar et al) [183]

Risk Factor		Points
Female Gender		1
Congestive Heart Failure		1
Left Ventricular Ejection Fraction <35%		1
Pre-operative Use of IABP		2
COPD		1
Insulin-requiring Diabetes		1
Previous Cardiac Surgery		1
Emergency Surgery		2
Valve Surgery Only (reference to CABG)		1
CABG + Valve (reference to CABG)		2
Other Cardiac Surgeries		2
Pre-operative Creatinine 1.2 to <2.1 mg/dl (reference to 1.2)*		2
Pre-operative Creatinine ≥2.1 (reference to 1.2)		5

Minimum Score = 0, Maximum Score = 17

*1mg/dl equivalent to 88.4µmol/l

Table 10: Risk factors from Finlay et al. [212]

Risk Factor		Description / Explanation
Age		>75 years
Hypotension		SBP <100 mmHg or decrease of ≥40 mmHg from usual baseline
Sepsis		Two or more criteria for SIRS due to suspected infection
Hypovolaemia		Suggested by history or on clinical examination
Chronic Kidney Disease		Stage 3-5 (eGFR <60ml/min/1.73 m2)
Vascular Disease		History of atherosclerotic vascular disease

Congestive Cardiac Failure		History of congestive cardiac failure or current presentation consistent with acute cardiac failure
Diabetes Mellitus		
Jaundice		Clinical or biochemical jaundice
Nephrotoxic Medication		Nephrotoxic medication used in the week prior to admission

There is however a paucity in the literature of studies regarding the risk and risk prediction of AKI in unselected emergency admissions to a district general hospital. Finlay *et al* published a recent study of AKI risk factors (Table 10) associated with AKI in patients admitted to acute medical units (AMUs) in a study conducted over two separate 24-hour periods at a total of 10 AMUs. [212] Forni and colleagues have developed a model for predicting acute kidney injury in a subset of medical patients admitted to a UK hospital. [213] Their model included some physiological markers.

The literature here and suggested risk factors for the development of AKI provide a basis and guidance for the development of risk models in this thesis (Chapter 5). As reported, the above risk analyses so far described in the literature are mainly restricted to defined populations, importantly following cardiac surgery or following the administration of contrast for radiological imaging. In the risk modelling developed and reported in this thesis, the population of analysis will be less restricted and instead represent an unselected in-hospital population.

Why develop risk models?

As discussed previously, the ultimate form of treatment is prevention of a disease process, and in the same way that we can use computing to effectively alert to the presence of acute kidney injury (AKI), can we use computing to determine a patient's risk of AKI, and then alert the clinician to this risk at the point of care? The answer to the latter in terms of alerting is answered above (see Chapter 3). But can we determine risk electronically?

With the increasing power of computing, and the wealth of data about a patient now available electronically, we can use this to determine risk. Data within the National Health Service (NHS) has now become more accessible with improved standardisation, partly to allow audit, comparison of activity, and also for financial determination.

It is now the case that every visit of a patient to secondary care services results in a database entry in the Trust Data Warehouse to include data such as; patient demographics (dob, age, gender) admission and discharge dates, admission from (for example home or residential care), consultant responsible for care, GP details, primary (often the reason for admission or primary diagnosis during the admission) and secondary (often past medical history) medical problems (standardised in the ICD-10 definition of diseases), type of admission (elective, emergency), and length of stay. All blood test results and microbiology testing and results are clearly stored in the pathology database. Discharge notifications, which are sent to primary care on discharge of a patient from hospital, including coding of the reason for admission, past medical history, and importantly the medications that the patient was discharged on, are all clearly recorded in the Trust Data Warehouse. All operations (standardised using the OPCS definition of procedures), the surgeon carrying out the procedure, the anaesthetist delivering the anaesthetic, the timing of the procedure and anaesthetic are all stored electronically. See appendix 7 for further details of the data sources used in the study here (Chapter 5). In some Trusts vital signs observations (blood pressure, pulse, temperature, oxygen saturations) of patients are now stored electronically.

All of these data sources can be used in real-time to determine the risk of a patient without the need to clinically assess the patient. For example, when a patient is admitted to A&E, without a doctor even reviewing the patient it is possible to extract electronically from previous hospital admission records as described above, the patient's age and gender, past medical history, medications on last discharge, all blood results and microbiology testing and results over the last year. This data can then be used instantly to determine risk, even more so

when combined with the reason for admission in this instance. As the patient moves through the pathway of admission, further data including acute blood testing, radiology investigations, operative procedures and vital signs observations can all be added to the background dataset to provide further information to determine risk of new AKI or of worsening AKI if already present.

Chapter Summary

The review of the literature here suggests a number of potential risk factors for AKI, which could be used to determine a patient's risk of developing AKI and hence predict which patients to focus management strategies to attempt to reduce / mitigate tis risk.

Key potential risk factors include; age, gender, level of care prior to admission, co-morbidity (importantly congestive cardiac failure, chronic obstructive pulmonary disease (COPD), diabetes, chronic kidney disease (CKD), vascular disease, liver disease), potentially nephrotoxic medication, sepsis, blood results as markers of infection / sepsis including white blood cell (WBC), c-reactive protein (CRP), positive microbiology results indicating infection / sepsis, surgical procedures, and vital signs observations (blood pressure, pulse, temperature, oxygen saturations).

How can we therefore use this data to predict which patients will develop new AKI, or if patients already have AKI, which of them will experience worsening AKI, in order for management changes to be instigated early to either prevent AKI or prevent worsening AKI? The answer is in risk modelling.

This literature provides a basis for variable selection for the risk modelling in Chapter 5. Table 11 documents the variables chosen for risk modelling, the literature available to support their selection and the scientific justification for their choice, particularly of importance for variables not previously reported in the literature.

Table 11: Variables chosen for risk modelling; description and scientific justification

Variable Name	Variable Description	Scientific Justification	References
Age	Age at admission.	In the majority of disease processes older age is found to be a risk factor – likely related to increasing co-morbidity and vascular changes with age. Evidence that with increasing age there is an increasing risk of AKI.	70, 180-184. 212.
Gender	Gender.	Reported gender discordance in AKI. Unlike most chronic kidney diseases, in AKI evidence a female gender has a higher risk for AKI.	180, 182, 183, 185.
Charlson co-morbidity score	A scalar measure of the degree of co-morbidity.	Individual co-morbidities confer risk of AKI. In modelling while each individual co-morbidity could be included, there may be small numbers in some groups, hence the use of a scalar measure of the degree of co-morbidity (the summation of the given weight for each co-morbidity), using validated algorithms and a modified Charlson co-morbidity score. The higher the score the greater the degree of co-morbidity.	CKD: 180-183, 186-192, 212. Cardiac disease and intervention: 183, 185, 192-199, 212. Heart failure: 200, 212. Diabetes: 70, 181, 201, 212. Chronic Lung Disease: 183. Chronic Liver Disease: 182, 190. Myeloma: 202, 203. Malignancy: 204. Defining the modified Charlson co-morbidity score: 101, 102, 214.
Primary diagnosis	The reason (diagnosis) for admission.	It would be expected that the underlying disease process is likely to predict the development of AKI. Some disease processes (for example sepsis) are likely to have higher risks of AKI, however the need for admission (hence degree of sickness) in	Sepsis: 212. Jaundice: 212.

		general is likely to be an overriding risk.	
Medications	Prescribed medications – assumed from medications on previous discharge summaries. Total number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics.	An increased medication burden at the time of exposure to another insult (e.g. operative intervention, contrast administration, sepsis) may restrict the body's response to protect renal perfusion and prevent AKI. Hence increase susceptibility to AKI.	ACEi / ARB, Diuretics, NSAIDs: 206-210. Nephrotoxic medication: 212.
Outpatient attendances in last 12 months	Number of outpatient appointments attended in the 12 months prior to admission.	A surrogate marker of co-morbidity. The greater the co-morbidity the patient has (and with this the greater the risk of AKI as above), the more likely they are to have outpatient attendances in respect of these co-morbidity. The greater the number of attendances the greater the co-morbidity or it could be hypothesized the more active / less controlled the co-morbidity requiring more frequent visits.	
Admission in last 30 days	Admission to hospital in the 30 days prior to this admission.	Defined as a re-admission (within 30 days) and hence may suggest an ongoing disease process which is not controlled.	
Admission in last 2-12 months	Admission to hospital in the 2-12 months prior to this admission.	A patient who has had admissions in the preceding year is likely to represent a patient who is unwell and is a surrogate marker for active disease.	
Alanine Transaminase (ALT)	A liver enzyme. Measured clinically to determine liver function. In the event	Causes of hepatocellular injury such as ischaemia in a hypovolaemic,	Chronic Liver Disease: 182, 190. Jaundice: 212.

	of acute hepatocellular injury, the ALT level rises.	hypoperfusional state, also results in a simultaneous kidney injury due to the same mechanisms. Other causes such as paracetamol overdose can also result in acute kidney injury. It would be expected clinically that a raised ALT would be associated with increased risk of AKI. In chronic liver damage and cirrhosis (again a risk for AKI), there may however be a reduced level of ALT as production of the enzyme is decreased. Hence a high or low ALT would be expected to be associated with AKI.	
Amylase (AMY)	An enzyme produced in the pancreas that aids with the digestion of carbohydrates.	A raised level of amylase can signify the presence of pancreatitis, which clinically would be expected to carry a risk of AKI.	
Brain Natriuretic Peptide (BNP)	An amino acid produced by the cardiac myocytes, when they are under strain, and in this way the BNP is associated with heart failure.	Heart failure, may result in reduced perfusion of the kidneys and thus carry a risk of AKI.	Heart failure: 200, 212.
Corrected Calcium (Ca)	A mineral in the blood, corrected for the albumin level in the blood.	Raised calcium can lead to dehydration which can result in AKI. Low calcium can also signify acute disease, which may have an increased risk of AKI. Raised calcium is also found in some malignancy in particular myeloma.	Myeloma: 202, 203. Malignancy: 204.
C-reactive protein (CRP)	A marker of infection or inflammation.	Infection and importantly sepsis carries a significant risk of AKI. The higher the CRP the greater the severity of the infection and it would	Sepsis: 212.

		be expected the higher the risk of AKI.	
Haemoglobin (Hb)	The iron-containing oxygen-transport metalloprotein in red blood cells.	A low Hb is a marker of acute or chronic disease and would therefore be expected to be associated with AKI.	
Glycated haemoglobin (HbA1c)	Gives an average of blood sugar readings over the last 120 days. A value greater than 6.5 indicates a patient with diabetes.	Patients with diabetes have an increased risk of AKI. A value greater than 7.5 indicates that the diabetes is not well controlled, and it would be expected that the higher the value, the worse the diabetic control, and the higher the risk of AKI.	Diabetes: 70, 181, 201, 212.
Potassium (K)	An electrolyte which is essential for the normal functioning of cells, importantly cardiac cells. Maintaining the gradient across the cellular membrane is essential, and changes in this can lead to cardiac arrhythmias.	The K level itself in blood would not be thought to have a causal relationship with the development of AKI, however a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance.	
Magnesium (Mg)	An electrolyte which is essential for the normal functioning of cells.	The Mg level itself in blood would not be thought to have a causal relationship with the development of AKI, but again a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance.	
Sodium (Na)	An electrolyte which is essential for the normal functioning of cells.	The Na level itself in blood would not be thought to have a causal relationship with the development of AKI, but again a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance. A low Na may also signify diuretic medication use.	Diuretics: 206-210. Nephrotoxic medication: 212.

Platelets (PLT)	A measure of the number of platelets in the blood. Platelets are essential for the clotting of the blood.	The PLT level itself in blood would not be thought to have a causal relationship with the development of AKI. However, a low platelet count may be related to haematological disease or acute illness, and a high platelet count may also signify acute illness and specifically inflammation / infection. In both of these instances an increased risk of AKI would be expected clinically.	Sepsis: 212.
White blood cells (WBC)	A direct marker of infection.	A low (<4) or high (>11) WBC can signify infection and an infection carries a risk of AKI.	Sepsis: 212.
Creatine kinase (CK)	A breakdown product of muscle.	When excess muscle breakdown occurs, high levels of CK can cause damage to the kidneys and result in AKI, a condition called rhabdomyolysis. It would therefore be expected that the greater the CK the greater the risk of AKI.	
Troponin	A cardiac enzyme released during cardiac muscular damage. Used to diagnose acute coronary syndrome (ACS).	Cardiac disease, intervention, and acute coronary syndromes (ACS) are risk factors for AKI due to the changes in perfusion related to the ACS and the intervention. The testing of troponin suggests a presentation with chest pain, and a positive troponin suggests an ACS.	Cardiac disease and intervention: 183, 185, 192-199, 212.
Blood culture	A culture of a sample of blood in an attempt to grow and solate pathogens and define sensitivity to antibiotics.	The sending of a blood culture suggests a patient has presented with a temperature, infection or overt sepsis, which carry a risk of AKI. It would be	Sepsis: 212.

		expected that this risk is greater if the culture is positive and grows a significant pathogen.	
Faeces culture	A culture of a sample of faeces in an attempt to grow and isolate pathogens.	The sending of a faeces culture suggests a patient has presented with diarrhoea / loose stools, which can lead to dehydration and volume depletion and hence would be expected to be a risk for AKI. A positive culture would be expected to be a further increase in risk.	Sepsis: 212.
Mid-stream specimen urine or catheter specimen urine	A culture of a sample of urine in an attempt to grow and solate pathogens and define sensitivity to antibiotics.	The sending of a urine culture suggests a patient has presented with a temperature, symptoms of urinary infection or overt sepsis, which carry a risk of AKI. It would be expected that this risk is greater if the culture is positive and grows a significant pathogen.	Sepsis: 212.
Sputum culture	A culture of a sample of sputum in an attempt to grow and solate pathogens and define sensitivity to antibiotics.	The sending of a sputum culture suggests a patient has presented with a temperature, symptoms of productive cough or overt sepsis, which carry a risk of AKI. It would be expected that this risk is greater if the culture is positive and grows a significant pathogen.	Sepsis: 212.
Swab, aspirate, pus culture	A culture of a sample of potentially infected material in an attempt to grow and solate pathogens and define sensitivity to antibiotics.	The sending of a swab, aspirate, pus culture suggests a patient has presented with a temperature, and the presence of infective material, for example a skin wound, a collection that can be aspirated, or overt pus discharge. The infective process would be expected to	Sepsis: 212.

		carry a risk of AKI particularly if overtly septic. It would be expected that this risk is greater if the culture is positive and grows a significant pathogen.	
Estimated glomerular filtration rate (eGFR) baseline	GFR is a marker of kidney function determined from measurement of serum creatinine and with the age and gender of the patient using a mathematical equation (in this case use of the Modification of Diet in Renal Disease (MDRD)) to estimate the GFR.	The eGFR is used in the definition of Chronic Kidney Disease (CKD), and hence is a marker of CKD which is known to carry a risk of AKI.	CKD: 180-183, 186-192, 212.
Proteinuria	A measurement of the quantity of protein in the urine. In the healthy, normal kidney there should be no protein in the urine.	Here, proteinuria is used as a marker of CKD which is known to carry a risk of AKI.	CKD: 180-183, 186-192, 212.
Number of contrast radiology scans	The number of scans the patient has experienced in the week prior to admission, or during admission that involve the exposure to intravenous contrast.	There has long been understood a relationship between the exposure to intravenous iodinated contrast agents and the development of AKI, usually within 72 hours of administration of the contrast. This is a leading cause of hospital-acquired AKI but has reduced with the use of iso-osmolar iodinated contrast medium and pre-hydration.	Contrast nephropathy: 200.
Operative severity score	Each procedure a patient underwent during admission was coded using the OPCS Classification of Interventions and Procedures. Two clinicians; Dr Michael Bedford and Professor Chris Farmer independently coded each procedure in the	An operative intervention which may result in hypovolaemia and hypotension, blood loss, retention of urine post operatively, and a risk of infection, would be expected to confer a risk of AKI. The more invasive the procedure and greater the length	Cardiac disease and intervention: 183, 185, 192-199, 212.

	database with a severity score ranging from 1 (least severe) to 5 (most severe). (see Appendix 7, Table 49).	of anaesthetic the greater the risk of AKI that would be expected. This risk has previously been investigated in cardiac surgery with the development of risk scores for the development of AKI in this setting.	

Chapter 5: Developing a risk model and clinical algorithm for AKI

Aims

The aim of this chapter is to develop a risk model / models for the prediction of new or worsening AKI, validate these models, and suggest a clinical algorithm to employ these models at time points in a patient's hospital admission to inform clinical decision making.

Methods

Design and theoretical/conceptual framework

Quantitative methodology in the form of traditional risk modelling techniques were employed to both formulate predictive risk models, and to validate these models in the local / index population of East Kent, and in a second population at Medway NHS Foundation Trust.

This quantitative methodology / analysis was conducted alongside the qualitative analysis to determine the appropriate methods to deliver the results of risk modelling to the point of care described in Chapter 3.

Funding

The risk analysis study here was funded by a grant from the National Institute for Health Research (NIHR) Health Services and Delivery Research (HS&DR) Researcher-Led work-stream (11/2004/28: Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission) (see report abstract - Appendix 8).

Setting / Context

For risk model development and validation in the first population the study population included all patients presenting to the three acute hospitals of East Kent Hospitals University NHS Foundation Trust (EKHUFT); Kent and Canterbury Hospital in Canterbury, William Harvey Hospital in Ashford, and Queen Elizabeth the Queen Mother Hospital in Margate, in the calendar year of 2011. Maternity admissions and elective admissions were excluded. While elective admissions to hospital should by their very nature (clinically more stable patients) have a significantly lower risk of developing acute kidney injury (AKI) during admission, or even less so having AKI at the point of admission, there is still a risk present. For example, a patient undergoing elective major abdominal or cardiac surgery, which carry a significant risk of AKI. However, the analysis here was focused on emergency admissions to hospital. It may be that following this work, further models and clinical algorithms for elective admissions should be developed, informed by the work here.

The renal tertiary referral centre is based at Kent and Canterbury Hospital. The secondary validation population included all patients presenting to Medway NHS Foundation Trust over the same time period and with the same exclusions.

Research Governance

The project received full ethical approval from the Kent Research Ethics Committee (**reference 10/H1101/89**) on 20/12/2010. This approval was for patients in East Kent. Subsequently a substantial amendment was submitted on 16/06/2011 to the research ethics committee to include validation of the risk model in the Medway (Medway NHS Foundation Trust) population, and this was formally approved on 13/07/2011. The Project was also reviewed and had agreement of methods from the National Information Governance Board (NIGB). The ethical considerations in this study were:

- ***Consent:*** The risk model development involved retrospective assessment of patient data of all admissions to hospital over a 12-month period. For a retrospective analysis of this type, it would not have been appropriate or

practical to seek consent from all patients previously admitted to hospital. The study had the support and endorsement of the Medical Director and Chief Executive of the EKHUFT and the Primary Care Trust (PCT) and the Trust Patient Safety Board.

- ***Confidentiality:*** Patient information was extracted and stored anonymously under a unique identification number on a secure server. Confirmation was obtained from the Caldicott Guardian that the study satisfied the Information Governance issues of confidentiality and data security.

There were no potential risks or burdens for research participants as the risk model development used retrospective data.

Public and Patient Involvement

Prior to this study, and importantly in the design process, advice was sort from patient representatives. During the study however, due to the nature of the study being a mathematical analysis of retrospective data, there was limited public and patient involvement.

Data Collection

Prior to study commencement and funding applications an assessment had been made of the data set available for the study in terms of database access and variables available.

The source data was stored in the trust data warehouse with all systems utilising a relational database structure and managed with the 'Structured Query Language' (SQL), except for the pathology data which was held in an Oracle (Oracle Corporation) object-relational database management system. Time was spent analysing each database to determine:

1. An identifier in order to define data unique to a given patient. It was determined that the best identifier to utilise would be the NHS number. The NHS number is unique to a patient and allowed linkage of datasets. One limitation of the use of NHS number is when a patient is admitted to the hospital and the NHS number is not known to the Patient Administration System (PAS). This may be for a number of reasons; 1) the patient has not been seen / had an episode of care before at the hospital, in which case a request is put through to Open Exeter and the data held on the National Health Application and Infrastructure Services (NHAIS, as part of NHS Digital) to look up the patient and their demographic data and linking this to provide their NHS number. This would usually be achieved during the patient's inpatient stay or shortly afterward during clinical coding and so in a retrospective database study such as this, the NHS number in these patients should be available at the time of data extraction. 2) the patient does not have an NHS number. This may be possible if a patient is visiting the country from abroad, or is migrant from another country and has not registered with primary care. While this patient may be present on the hospital system for the specific admission it is therefore unlikely that they would have previous blood testing in the form of creatinine data in order to define AKI and so would be excluded from the analysis anyway. On choosing the unique identifier for a patient consideration also had to be given to, in terms of the robustness of this approach, the occurrence of this identifier in each database in order to allow linking of the datasets into one unique record for a patient in the study database. In each database the NHS number was the most robust and unique identifier to utilise. For this analysis data was extracted for the calendar year 2011. Following analysis of the pathology database which included both blood testing from primary and secondary care settings it was noted that following a change in order requesting and ordercomms in mid 2009 >99% of pathology records included the NHS number which could be used as the unique identifier. As the required limit of historical data for the extract and analysis was 12 months prior to the admission date, and the earliest admission in the dataset would be 01/01/2011, the earliest data required would be 01/01/2010 and therefore after the change in requesting in 2009. The NHS number could therefore again in this instance be used as the unique identifier to link the data (results) both within the pathology database and across databases.

2. Coding. Within each database a number of fields were populated with codes that required translation and interpretation prior to analysis. For example the primary and secondary diagnoses data were recorded by ICD-10 coding for standardisation. ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems from the World Health Organisation (WHO). There are more than 14,400 different codes and it became apparent that there were far too many codes to use as individual categories within either the primary or secondary diagnoses predictor variables in the regression analyses. Statistically there would have been too few values for each category of the variable to develop a model from. In order to narrow the categorisations of co-morbidity, validated coding algorithms from Quan et al,[101] with further validated algorithms for diabetes [102] and hypertension, were used to create lookup tables which allowed translation of a specific ICD-10 code into a higher level co-morbidity descriptive and also a score. The score could then be summated to determine the modified Charlson co-morbidity score for each patient. Within the hospital episode data tables lookup tables were also required to translate codes, for example admission location and discharge location (for example home, residential care, nursing care).

3. The required variables from each database and the source tables where these variables were located.

4. Data linkage between tables. In order to collate variables across multiple tables within the databases, time was taken to understand data linkage between tables which varied between databases, for example; trust internal numbers, episode numbers, NHS number, hospital number.

Following the above database analysis, Standard Query Language (SQL) queries and the Java programming language (Java is a computer programming language that is concurrent, class-based, and object orientated) were utilised by Mr Toby Wheeler (IT Application Manager, EKHUFT) in collaboration with myself to extract the required variables in the context of each patient. Data was extracted into a research database / table with each line (row) of data in the table representing an episode of care (hence a single patient may have multiple rows (episodes of care) in the dataset). For some variables for example demographic data there was a simple extract of variables for each episode of care. For other

variables such as blood results (for example c-reactive protein (CRP), haemoglobin (Hb)) the variables were extracted by coding / programming which included time constraints to determine the values to extract and place in the research database for that episode of care. For example the most recent result being the result within the last 30 days prior to hospital admission, or the 12 month average being the average of all values for that variable within the 12 months prior to hospital admission.

For the determination of acute kidney injury (AKI) the detection algorithm was provided by myself to Mr Toby Wheeler for coding / programming for data extraction. As described in the methods, the analysis in Chapter 2 and the initial analysis in Chapter 5 used an algorithm comparing the index creatinine under assessment to the baseline creatinine (which was determined as the lowest creatinine in the 12 months prior to admission) to detect AKI. The subsequent analysis in Chapter 5 utilised the NHS England national algorithm (Appendix 9) to define AKI. For each hospital episode of care all the creatinine results during admission and for the 12 months prior to admission were extracted and loaded into memory to allow definition of AKI with the above algorithms which were coded into computer programming by Mr Toby Wheeler. The values for AKI ('no AKI', 'AKI stage 1', 'AKI stage 2', 'AKI stage 3', 'missing data') were then placed into the row in the research database / table for each of the time points described in the methods, within that episode of care / admission.

Following completion of data extraction identifiers were removed including for example the NHS number and date of birth, and a unique study number was inserted, in order to pseudoanonymise the dataset in compliance with the ethical approvals, and also allow linkage to the original source datasets by the data custodian if required to ensure data integrity, again in compliance with the ethical approvals. The dataset was then frozen in this state for statistical analysis.

The following clinical systems / databases / datasets were available for data extraction:

Hospital Episode Data: The hospital data warehouse holds data from coded episodes of care on all admissions and outpatient activity in East Kent. From this data the Hospital Episode Statistics (HES), and the Secondary Uses Services (SUS) data that are collected nationally are derived. Importantly this dataset includes patient demographics (date of birth, age, gender, postcode), admission and discharge dates and times (from this calculated length of stay), and co-morbidity defined in terms of primary diagnoses (reason for hospital admission) and secondary diagnoses (representing either past medical problems or further in-hospital diagnoses). In this study the secondary diagnoses were classed as past medical problems, i.e. co-morbidity. A modified Charlson co-morbidity score was calculated using a modified version of the Charlson score developed by Dr. Foster™ Intelligence. [214]

A full list of variables available from this dataset are described in Appendix 7 (Table 44).

Pathology: The pathology database holds records of all blood tests in East Kent requested in primary care and in secondary care both in the outpatient and inpatient setting. All NHS blood testing results in the East Kent population are recorded on this database. This dataset therefore includes blood tests prior to and during a patient's admission, and importantly includes creatinine testing from which to define AKI.

The variables available, and thought to be of clinical importance, from this database are described in Appendix 7 (Table 45).

Definition of AKI:

AKI was defined by the AKIN criteria using the lowest serum creatinine (SCr) in the 12 months prior to the date of hospital admission as the reference after the method of LaFrance et al.[95] Of note the analysis here used serum creatinine criteria to define acute kidney injury. As described in Chapter 1 the urine output

criteria are more sensitive in detection, however this data is not available in a retrospective database analysis.

Electronic Discharge Notification: At East Kent Hospitals University NHS Foundation Trust (EKHUFT) all discharges from hospital are recorded on an electronic discharge notification (EDN) which includes a summary of the admission and the medications the patient is taking on discharge. This summary is sent to the General Practitioner (GP) in primary care at discharge to enable continuity of care. Therefore, at the point of hospital admission by reviewing previous EDNs, assumptions can be made as to the medications a patient is taking prior to admission.

The variables available from this database are described in Appendix 7 (Table 46).

Operation Data: Every operation performed in theatres at EKHUFT is recorded in an electronic operation database. The system records date and time of procedure, length of procedure, length of anaesthetic, surgeon and anaesthetist, name of procedure, and the ICD-10 and READ code for the procedure, and the subjective ASA score, for the patient determined by the anaesthetist (Appendix 7).

Two clinicians; Dr Michael Bedford and Professor Chris Farmer independently coded each procedure in the database with a severity score ranging from 1 (least severe) to 5 (most severe), informed by the National Institute for Health and Care Excellence (NICE) guidance; Pre-operative tests: The use of routine pre-operative tests for elective surgery. [215] Where differing opinions of severity for a procedure existed between the two clinicians, these were discussed and a final severity score determined.

The variables available (Table 47) in this database, and defined operative score (Table 49) are documented in Appendix 7.

Data Analysis

The main aim of the study presented in this chapter was the development of predictive models for identifying and stratifying the risk of AKI at the point of and during hospital admission. These models included a large set of potential risk factors identified from secondary care records as well as admission characteristics of each patient. Traditional modelling techniques were employed in order to develop these models.

Points of Decision Making

The study is designed to develop and validate risk models to define risk of AKI or of worsening AKI during hospital admission. While risk models can be employed at any point during hospital admission, as data becomes available, as was clear from the qualitative analysis presented in Chapter 3, it is key that such alert of risk is delivered to the right person at the right time in order to inform and influence clinical decision making and add value to the patient's care. It was determined therefore that there were three time points during a patient's hospital admission where significant clinical decision making takes place at which the use of risk models would have greatest impact on clinical care and patient management. These time points are:

1. ***The point of admission to hospital (Model 1; see Figure 33):***

   The model applied in this case (referred to as Model 1) uses all electronic data up until the point of admission (and the reason for admission to hospital), to determine the risk of a patient already having AKI on admission, and in this way the model is guiding the testing of kidney function to ensure that patients who are likely to have AKI have their kidney function tested to unmask the condition and allow efficient appropriate clinical intervention to treat the acute kidney injury.

2. ***After 24 hours of admission (Model 2 and 3; see Figure 33):***

   The model here uses all electronic data both prior to admission to

hospital and up to 24 hours into the admission to determine the risk of developing AKI (referred to as Model 2), or of worsening AKI (referred to as Model 3) in the first 72 hours of admission. At this point (24 hours) patients are likely to be admitted to a ward or clinical decision unit / medical admissions unit and are likely to then be reviewed by the admitting clinical team on the post take ward round, or by the ward team on their ward round of new patients, providing another clear point of intervention. This will then guide clinical management at this point to define patients at risk of AKI that require:

1. management changes to include the stopping of nephrotoxic medication, fluid assessment and ensuring fluid repletion, monitoring of blood pressure and ensuring adequate blood pressure and appropriate use of anti-hypertensives.

2. daily renal function testing to observe for the development of AKI. If there is consideration at this point of discharge from hospital, the models at this point may inform the decision on discharge or if discharge is still intended then to guide follow up in primary care to observe for AKI (and also management of medications that may have been stopped temporarily while the risk of AKI exists).

3. ***After 72 hours of admission:*** The purpose of this model was to predict patients who would develop AKI, or worsening AKI if already present, during the rest of the hospital admission. During the progress of the study advice from clinical experts on the board of the NIHR HS&DR grant project (informed by results of risk modelling) determined that this point of risk assessment would not add clinical benefit for a number of reasons:

1. The risk models at this point were not sufficiently accurate to determine risk and guide clinical management, in part related to and a consequence of the fact that:

2. Most patients remain in hospital for less than 3 days (72 hours). For those who do stay in hospital over 72 hours this may range from 3 days up to as high as 90 – 365 days. In this case it is very difficult to determine risk of developing AKI in a widely varying time period, most importantly because these patients will develop new conditions and changes in blood results (variables in the risk models) after 72 hours which change their risk and cannot be accounted for at the point of modelling.

Clinical Alerting

The purpose of risk modelling developed and validated here are to inform and ultimately improve the clinical management of these patients at risk. This will be achieved by alerting to clinicians at the point of care, via systems described and developed in Chapter 3. The clinical alerting system will not solely alert to risk of AKI, but will also alert to patients with established AKI and provide clinical guidance to improve the management of these patients and reduce both the progression of AKI and the development of resultant sequelae. It is therefore important that both alerting to AKI and alerting to AKI risk are brought together into a clinical practice algorithm (Figure 33) to both guide alerting and also the clinical management pathway following an alert.

Alerting at the point of admission (Figure 33): Initial risk model development for the point of admission included pre-admission AKI as a variable in the model. As would be expected clinically, if a patient has AKI just prior to admission then they have a high risk that they will still have AKI at the point of admission. Initial models developed confirmed that the variable 'pre-admission AKI' was by far the strongest predictor of AKI on admission and diluted other variables in the model. As part of the clinical practice algorithm, the decision was

therefore made that all patients with pre-admission AKI should be alerted by the alerting system as 'pre-admission AKI', irrespective of risk assessment. In these patients, renal function testing should always occur on admission, and the management changes above should be implemented. Patients with pre-admission AKI were therefore removed from the admission models to predict AKI and hence the population of assessment for the point of admission models included only patients either without pre-admission AKI or patients who did not have pre-admission AKI status determined as they did not have renal function testing in the pre-admission period.

Alerting after 24 hours of admission (Figure 33): For patients who have AKI apparent on admission renal function testing, the clinical alerting system will alert to the presence of AKI, and suggest appropriate management interventions as described above, including daily renal function testing. Again as part of the clinical practice algorithm, patients with AKI on admission were therefore removed from the risk models at 24 hours to predict AKI at 72 hours, as the management changes will already be alerted by the system for these patients. Also including AKI on admission as a variable in a model to predict AKI at 72 hours would be highly predictive and dilute other variables and reduce the clinical utility of the system, especially as these patients will already be alerted by the system anyway, (Figure 33).

This led to the development of the clinical practice algorithm (Figure 33) to guide:

- AKI alerting
- Definition of the patient populations to be assessed by the risk models described in this chapter and defined above; at the point of admission and at 24 hours into admission, to define and allow alerting of patients at risk of AKI
- Appropriate renal function testing
- Appropriate management interventions

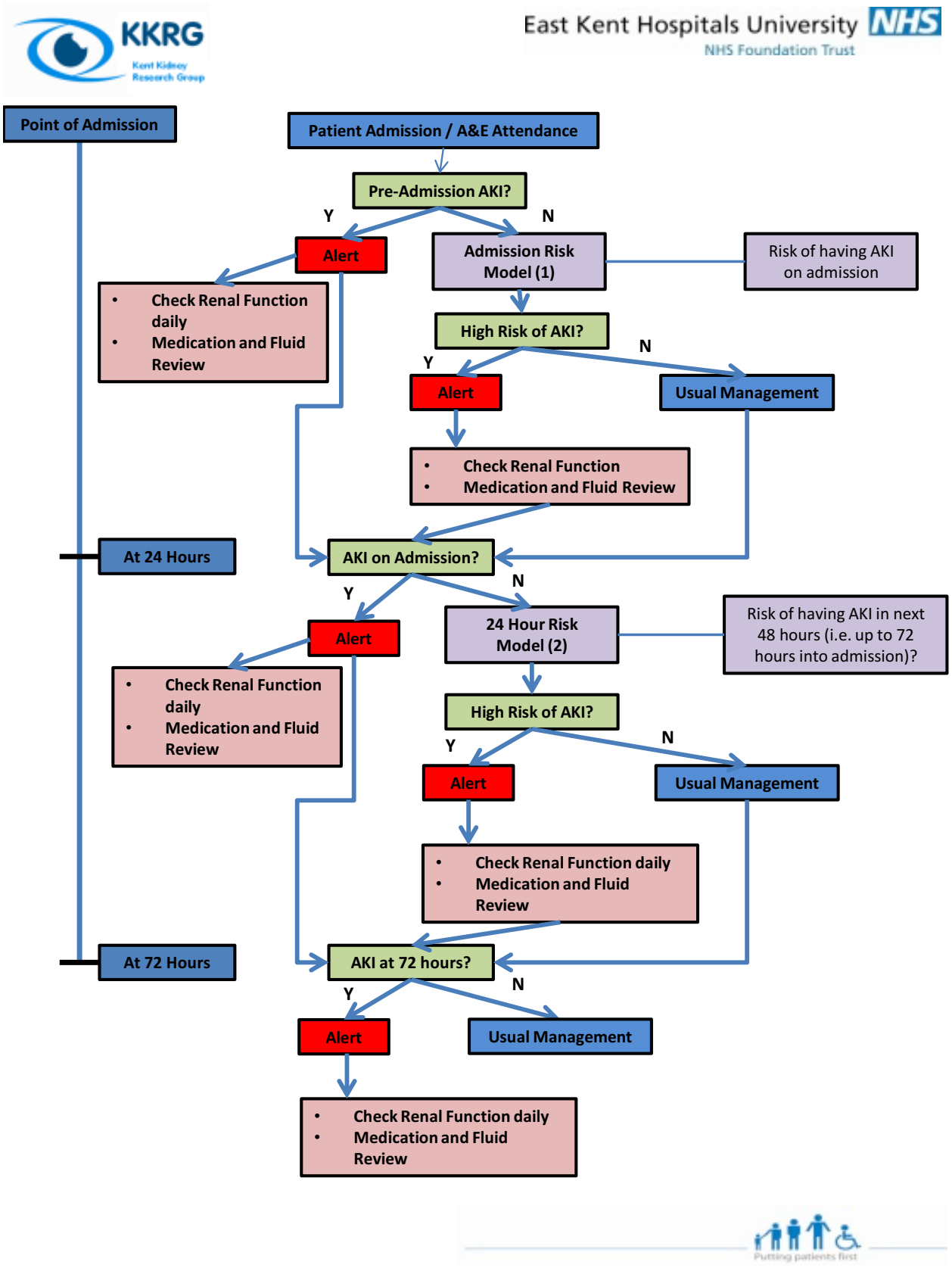


Figure 33: Acute Kidney Injury (AKI) clinical practice algorithm to define points during a patient's hospital admission to develop and employ risk models to define risk of AKI.

Risk Model Development and Statistical Analysis Methods

Stata (version 12.1) was used for development of the following models. The use of Stata was performed by Mr Paul Bassett (Stats Consultancy Limited), with variable selection, data interpretation and method determined by Dr Michael Bedford in collaboration with Mr Paul Bassett.

Variable Relationships

As described above, based on variable availability within the given databases and informed by clinical opinion, the literature review in Chapter 1, epidemiological analysis presented in Chapter 2, and the literature review in Chapter 4, variables were selected for inclusion in the analysis (see Table 11, Chapter 4 and Appendix 7 for variable definitions).

The first stage of risk modelling was to determine relationships between risk factors and the outcome variable acute kidney injury (AKI). This was of key importance for pathology blood tests. For each of these, a univariable analysis was performed to create a plot of the blood test value on the x-axis against risk of AKI on the y-axis.

In order to simplify model development, the pathology blood tests as continuous variables were converted into categorical variables with the categories: 'not tested', 'normal', 'abnormal'. While each blood test has a 'normal range' defined by the laboratory, in an attempt to be specific for 'normality' in terms of these variables in relation to AKI, the plots described were assessed to define points at which each variable became associated with AKI to define 'abnormal' and hence also 'normal' ranges for each variable.

Risk Model 1: The point of admission to hospital

As described above, risk Model 1 was to be developed and employed at the point of admission to hospital. The risk model development included emergency admissions to the three hospitals of East Kent Hospitals University NHS Foundation Trust (EKHUFT) during the calendar year of 2011.

Non-emergency admissions (i.e. elective admissions), admissions associated with pregnancy and childbirth, patient admissions without a creatinine blood test on admission (i.e. therefore unable to define the outcome variable, AKI on admission), and patient admissions with pre-admission AKI (as described above) were excluded from the analysis in risk Model 1. Patient admissions in which pre-admission AKI could not be defined (i.e. no creatinine blood test available in the pre-admission time period) remained in the analysis and hence were treated as not having pre-admission AKI.

The included patient admissions in the analysis were randomly (using pseudo-random numbers) allocated to either a 'development' dataset which was used to construct the model, and a 'validation' dataset which was used to test and validate the derived models within the same demographic population. This allocation was performed in a 3:1 ratio of development to validation to allow a larger dataset for development.

As described, the outcome variable for risk Model 1 was acute kidney injury (AKI) on admission. This was considered as an ordinal. An ordinal variable is a variable in which there are ordered categories (an ordinal scale) in this case the stages of acute kidney injury (AKI); 'no AKI', 'AKI stage 1', 'AKI stage 2', 'AKI stage 3'. With an ordinal outcome measure the traditional risk modelling analysis here was therefore performed using ordinal logistic regression. Ordinal logistic regression is as the name suggests a form of logistic regression that deals with an outcome / dependent variable which is ordinal in nature. Hence the outcome variable has ordered categories, in this case the stages of AKI. As discussed in Chapter 2, logistic regression utilises a logistic function (the cumulative logistic distribution) to estimate probabilities and determine the relationship between and the effect of the independent variables (in this case the predictors such as age, co-morbidity, gender etc.) on the dependent outcome variable which is this case is the stage of acute kidney injury (AKI).

From review of the dataset it was apparent that a patient may have a number of admissions to hospital during the one-year study period and hence contribute to the dataset a number of times. This was addressed in the analysis using robust standard errors. The purpose of robust standard errors and robust regression methods is to allow estimate adjustments that account for biases in the dataset. In this case the fact that a single patient may have a number of admissions to hospital during the one year study period and hence contribute to the dataset a number of times. These multiple admissions in a single patient are not independent and hence can lead to bias. The use of robust standard errors tries to correct / account for this. There are a number of methods used in determining robust standard errors. The statistical package used here (Stata) uses the Huber-White Sandwich method.

At first a series of univariable analyses were performed to identify the association between each variable and the outcome measure of AKI. Following this a multivariable analysis was performed to assess the combined association between variables and the outcome of AKI.

An important question in all analyses is the treatment of missing data, which can be either at random or not at random. In medicine this can often be further complicated by being a known, or unknown, combination of the two. In this data set / analysis some variables such as the key demographics of age and gender were complete with no missing data. The variable 'primary diagnosis' included missing data and the decision was made to exclude patients from the analysis who did not have a coded 'primary diagnosis'. For the blood test variables missingness is less clear. In some cases, it may be that a patient has not had a specific blood test performed, which would have been abnormal had it been tested. This may be due to error on the part of the clinician, or sometimes failure of the test in the laboratory. This could be assumed as missing at random. For most blood tests however the missingness is a combination of missing at random, and more importantly the fact that a result is missing may be informative. For example, an amylase blood test (a pancreatic enzyme often used to define pancreatitis) is usually only tested in patients presenting with

abdominal pain, which could be a patient group with an increased risk of acute kidney injury (AKI), even more so if the amylase value is raised ('abnormal'). This would therefore suggest differing risks for the categories: 'not tested', 'tested and normal', 'tested and abnormal'. These categories were therefore defined and used in the analysis.

Collinearity was also assessed. Collinearity is when two or more of the predictor variables in the regression analysis / model are highly correlated, suggesting that one can be predicted from the others. For example the testing (or presence of a test for) white blood cells (WBC) and haemoglobin (Hb) are likely to be correlated as these tests are usually if not always ordered together in clinical practice as part of a full blood count (FBC). This collinearity does not affect the overall predictive ability of the model, but does affect results for individual predictors and so cannot accurately determine the effect of a given predictor.

In order to assess the degree of collinearity between predictor variables in the analysis, variance inflation factors were used. Variance inflation factors provide a measure of the extent to which the variance of a regression coefficient increased because of the presence of collinearity.

Where collinearity was demonstrated variables were either excluded from the analysis or combined in order to address this.

In order to retain only the statistically significant variables in the final model, a backwards selection procedure was employed. The process of backwards selection involves starting with all potential predictor variables in the model and then systematically removing each predictor variable in turn and assessing whether the predictive ability of the model is improved by the absence of that variable in the model. The predictor variable that improves the model the most when deleted is then excluded from the model permanently. This process is continued until there is no further improvement in the predictive ability of the model by removing any of the remaining predictor variables and we are left with the final model which retains only the statistically significant predictor variables.

Results are provided as odds ratios with statistical significance determined with the use of p-values. The purpose of an odds ratio is to provide a measure of the association between a given exposure (for example a patient having a given co-morbidity or having an operation) and the outcome of interest (in this case acute kidney injury (AKI)). The odds ratio is the odds of an outcome (for example AKI) occurring in the presence of a defined exposure (for example a given co-morbidity), in comparison to the odds of the outcome occurring in the absence of that exposure.

In the regression analysis used in risk modelling here, the regression co-efficient is an estimation of the increase in log odds of the outcome variable, per unit increase in the exposure / predictor variable. Hence the exponential of the regression coefficient describes the odds ratio (OR) related to a one-unit increase in the predictor variable. An odds ratio equal to 1 suggests that exposure to a given predictor variable (for example a given co-morbidity or operation) does not affect the odds of the outcome (in this case acute kidney injury (AKI)). An odds ratio of greater than 1 suggests that a given exposure is associated with a greater odds of a given outcome. An odds ratio of less than 1 suggests that a given exposure is associated with a lower odds of a given outcome.

The p-value is commonly used in traditional statistical methods and is in essence the probability of producing a result that is either equal to or greater than that which was actually observed when the 'null hypothesis' is true. The significance level (of whether a result (or difference between outcomes) is defined as significant) is commonly set at 5%. If the result of the p-value is less than or equal to this significance level then the results are not consistent with the 'null hypothesis' and hence the 'null hypothesis' is rejected and the result / difference is defined as statistically significant.

Risk Model 2: Predicting New AKI at 72 Hours

The purpose of risk Model 2 (as described above) is to predict patients who will develop new (i.e. not present on admission to hospital) acute kidney injury (AKI) in the first 72 hours of admission to hospital. The data used for the analysis includes all available variables pre-admission and up to the end of 24 hours into the admission, with the outcome variable being AKI at 72 hours. AKI at 72 hours was defined from the peak creatinine within the time period 12 hours post admission to 72 hours post admission time (see Appendix 7).

Non-emergency admissions (i.e. elective admissions), admissions associated with pregnancy and childbirth, patient admissions without a creatinine blood test within 12-72 hours post admission (i.e. therefore unable to define the outcome variable of AKI at 72 hours), patient admissions with pre-admission AKI as described above, and in this model patient admissions with AKI at admission, were excluded from the analysis in risk Model 2. As in risk Model 1 patient admissions in which pre-admission AKI could not be defined, and in addition in risk Model 2 patient admissions in which AKI at admission could not be defined, remained in the analysis.

As in risk Model 1 the full dataset for this analysis was split into 'development' and 'validation' datasets, and the outcome variable of AKI at 72 hours was considered as an ordinal measure as previously.

The statistical analysis was performed as described for risk Model 1.

Risk Model 3: Predicting Worsening AKI at 72 Hours

The purpose of risk Model 3 (as described above) is to predict worsening AKI in the first 72 hours of admission, in patients who have either AKI stage 1 or AKI stage 2 on admission to hospital. Although patients with AKI stage 3 on admission could experience a worsening AKI with a rising creatinine following admission, in terms of the ordinal definition of AKI they cannot experience a

worsening AKI from a start point of AKI stage 3 and so these patients were excluded from this analysis.

For this analysis non-emergency admissions (i.e. elective admissions), admissions associated with pregnancy and childbirth, patient admissions without a creatinine blood test within 12-72 hours (i.e. therefore unable to define the outcome variable of AKI at 72 hours), patient admissions with 'no-AKI' on admission, and patient admissions with AKI stage 3 on admission were excluded from the analysis in risk Model 3.

Again the full dataset for risk Model 3 was split into a 'development' and a 'validation' dataset as described in risk Model 1.

In this model the outcome variable was worsening stage of acute kidney injury (AKI) as a binary. Worsening stage of AKI therefore encompassed patients in whom AKI stage 1 was present on admission and worsened to stage 2 or 3 in the first 72 hours, or those patients in whom AKI stage 2 was present on admission and worsened to stage 3 in the first 72 hours of admission.

In this model in contrast with Models 1 and 2, due to the binary nature of the outcome variable, analysis was performed using multi-level logistic regression. Multi-level statistical methods (two-level models with admissions nested within patients) were employed to address the issue that a patient may have a number of admissions to hospital during the one-year study period as described previously.

Again as with Models 1 and 2, a series of univariable analyses were initially performed and following this a multivariable analysis.

Risk Model Validation

Validation in this population

As described, the full datasets for each model analysis were split at random into a 'development' (in-sample estimation) and a 'validation' (out-of-sample prediction) dataset with a 3:1 ratio development:validation. Hence, 75% of each model dataset was used to develop the model and then this model was validated in the remaining 25% of the dataset. This is therefore validation within the same population.

For validation of the model in each case, two features were assessed. Firstly, the ability of the model to discriminate between patients/patient admissions with a low risk of AKI and those with high risk of AKI. Secondly, the model calibration in terms of a comparison of the risk of AKI from the fitted model with that in the observed data.

As described for Models 1 and 2, the outcome variable of acute kidney injury (AKI) was defined as an ordinal variable with four possible values: 'no AKI', 'AKI stage 1', 'AKI stage 2', or 'AKI stage 3'.

While the models developed can be employed to derive predicted probabilities of a patient/patient admission being in each of the four categories, a four-point scale makes validation more difficult. Therefore, in order to simplify validation, the probabilities of AKI stage 1, 2 and 3 were combined to provide the probability of 'any AKI'. This was compared to the actual occurrence of AKI in the data.

In a second analysis, the probabilities of 'AKI stage 2' and AKI stage 3' were combined (and therefore 'AKI stage 1' was grouped with 'no AKI'), to provide the probability of developing 'AKI stage 2 or 3'. This was then compared to the actual occurrence of the composite AKI stage 2 or 3 in the dataset.

Three methods were employed for validation. Firstly, the categories: 'any AKI and 'AKI stage 2 or 3' were split into four risk groups based on predicted probabilities. For 'any AKI' the risk groups were $\leq$10%, 10-20%, 20-40% and >40%. For 'AKI stage 2 or 3', the risk groups were $\leq$2%, 2-5%, 5-10% and >10%.

Firstly, to assess the discrimination and calibration of the model, the expected occurrence of each of the risk groups was compared to the observed. Secondly, the 'Area Under the Receiver Operating Characteristic' curve (AUROC: equivalent to the c-statistic) was plotted and calculated in order to assess the discrimination between low and high-risk cases.

Values from the AUROC can be interpreted as:

0.5 - 0.6: No discrimination
0.6 - 0.7: Poor
0.7 - 0.8: Fair
0.8 - 0.9: Good
0.9 - 1.0: Excellent

The receiver operating characteristic (ROC) curve is a graphical illustration / representation of the performance of the model to predict / discriminate between high and low risk cases (in this case the risk of acute kidney injury (AKI)), and the change in this performance with variation of the discrimination threshold. In other words this process assesses the ability of the model to classify / predict a patient as high or low risk of developing AKI. On the graph, at each discrimination threshold the sensitivity (true positive rate) is plotted against 1-specificity (false positive rate). In order to summarise the visual representation of the ROC curve, the area under the receiver operating characteristic (AUROC) curve is used. This is equivalent to the c-statistic. The AUROC is the probability that the model being assessed will rank a randomly chosen positive instance (to develop AKI) higher than a randomly chosen negative one (not to develop AKI).

Thirdly, the Hosmer-Lemeshow test was employed to assess the difference between the outcome predicted by the model and the actual observed outcome, and hence an assessment of goodness of fit of the regression / risk prediction model. Again, for this test the dataset was divided into the categories and risk groups described above and the predicted number and observed number in each

category compared. In this test a good fit of a model to the data is suggested by a non-significant result, as this demonstrates that there is little difference between the expected and the observed numbers, and the model can be defined as well calibrated. The Hosmer-Lemeshow test is in essence a chi-square goodness of fit test. It is sensitive to slight differences between predicted and observed frequencies and is also highly dependent on the groupings chosen and hence this must be taken into account when using it as a validation tool.

Validation in a second population

The population demographic in East Kent is older and has less ethnic minorities than the general population of England. It is therefore important that the models developed from the East Kent population are validated in a second population, to assess the generalizability of the models across the National Health Service (NHS).

The second demographic population was chosen to be all patients presenting to Medway NHS Foundation Trust over the same time period as the East Kent population, the calendar year of 2011. Medway has a significantly younger population with greater ethnic minorities in comparison to the East Kent population. The same exclusions applied to the Medway population as to the East Kent population for the model development, with one variance in the data set. For the period of study, the calendar year of 2011, Medway NHS Foundation Trust did not use an electronic discharge notification system and so medication data was not available for analysis in this population.

Results

Risk Modelling Analysis

Variable Relationships

The first stage of risk modelling was to determine relationships between risk factors and acute kidney injury (AKI). This was carried out following the

definition and extraction of appropriate variables for the model. Of key importance was assessing the relationship between pathology blood test results and AKI. A univariable analysis was performed to create a plot (see results below) of the blood test value on the x-axis against risk of AKI on the y-axis. Once a normal range had been established for each variable, these variables could be converted from continuous to categorical with the categories 'not tested', 'normal' and 'abnormal'. Rather than simply using the laboratory normal range the point at which each variable became associated with AKI was used (based on the following univariable analyses and plots), however in the majority of cases this assessment agreed with laboratory normal ranges.

Below are each of the pathology blood test variables, a described clinical context to explain expected or clinically understood relationships with acute kidney injury (AKI) and the actual observed relationships with AKI in this dataset.

ALT (Alanine Transaminase)

ALT (Alanine Transaminase) is a liver enzyme. It is often measured clinically to determine liver function. In the event of acute hepatocellular injury, the ALT level rises. Causes of hepatocellular injury such as ischaemia in a hypovolaemic, hypoperfusional state, also results in a simultaneous kidney injury due to the same mechanisms. Other causes such as paracetamol overdose can also result in acute kidney injury. Here it would be predicted clinically that a raised ALT would be associated with an increased risk of AKI. In cases of chronic liver damage and cirrhosis, there may however be a reduced level of ALT as production of the enzyme is decreased. The relationship between ALT and AKI in this dataset (see below graph), suggest that only a low ALT is associated with an increased risk of AKI.

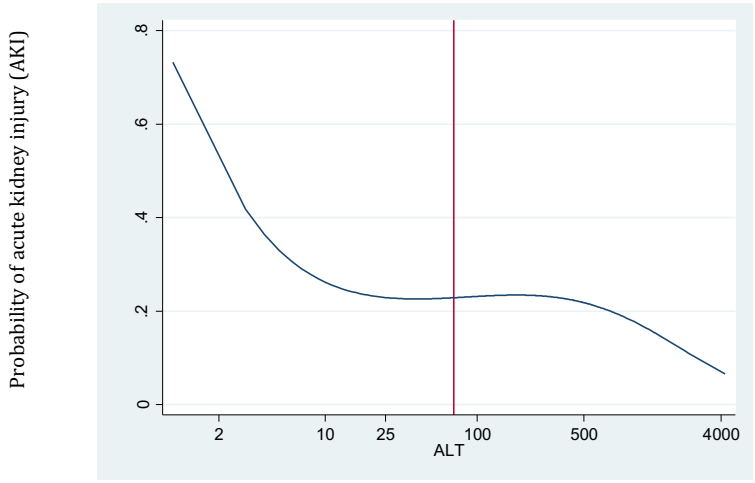


Figure 34: Relationship between alanine transaminase (ALT) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 0 – 70 U/l

Range determined as normal for risk modelling = ≤50 U/l

AMY (Amylase)

AMY (Amylase) is an enzyme produced in the pancreas that aids with the digestion of carbohydrates. A raised level of amylase can signify the presence of pancreatitis, which clinically would be expected to carry a risk of AKI. However, as shown in the graph below the relationship between AMY and AKI in this dataset, suggest that only a low AMY is associated with an increased risk of AKI.

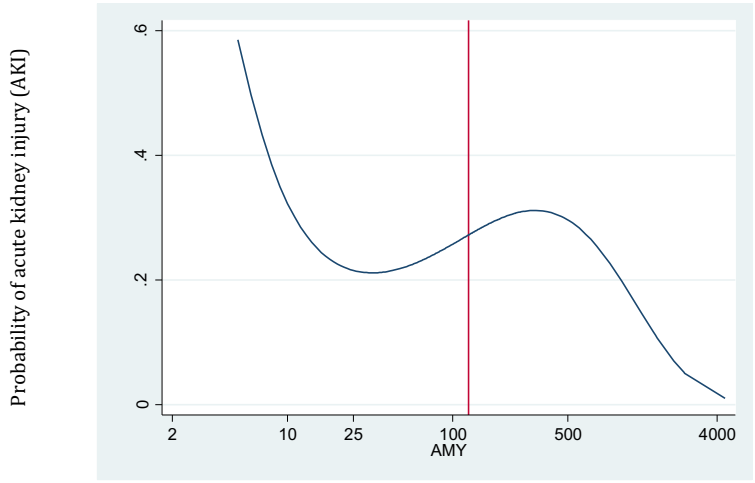


Figure 35: Relationship between amylase (AMY) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 0 – 125 U/l

Range determined as normal for risk modelling = ≤125 U/l

BNP (Brain Natriuretic Peptide)

BNP (Brain Natriuretic Peptide) is an amino acid produced by the cardiac myocytes, when they are under strain, and in this way the BNP is associated with heart failure. Heart failure, may result in reduced perfusion of the kidneys and thus carry a risk of AKI. The relationship between BNP and AKI in this dataset (see below graph), suggests that with a rising BNP value there is an increasing risk of AKI, above a BNP of 25.

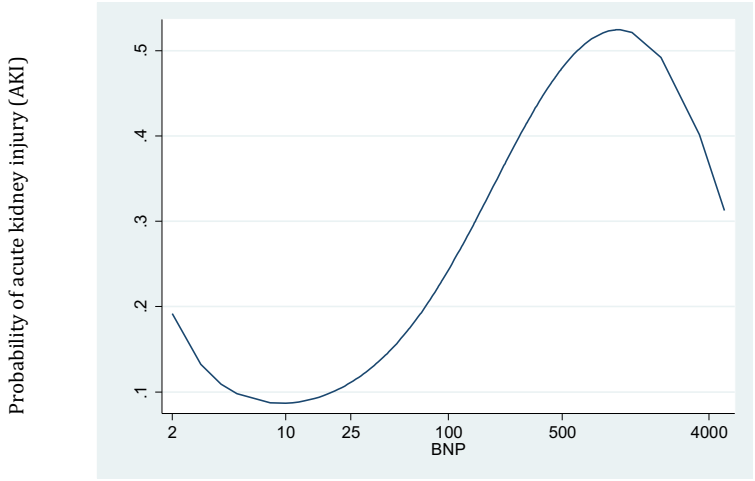


Figure 36: Relationship between brain natriuretic peptide (BNP) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 0-99 ng/l

Range determined as normal for risk modelling = ≤25 ng/l

Ca (Corrected Calcium)

Ca (Corrected Calcium) is the calcium, a mineral in the blood, corrected for the albumin level in the blood. Raised calcium can lead to dehydration which can result in AKI. Low calcium can also signify acute disease, which may have an increased risk of AKI. The relationship between Ca and AKI in this dataset (see below graph), suggests that both a low calcium and a high calcium have an increased risk of AKI and that risk increases the further away the value is from the normal range.

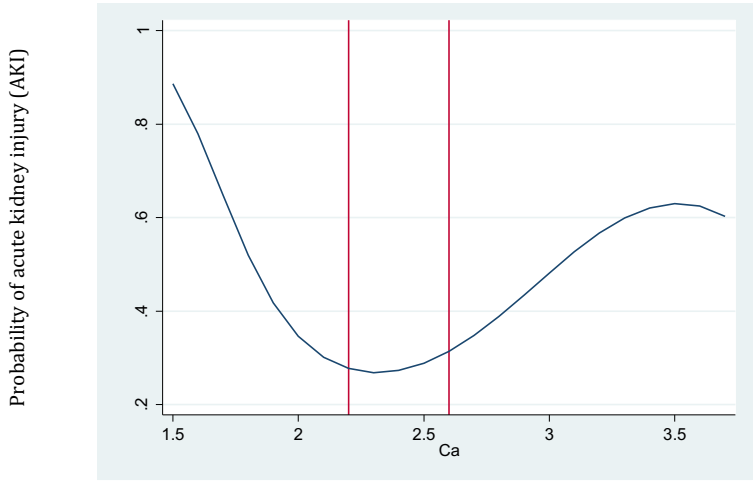


Figure 37: Relationship between corrected calcium (Ca) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 2.2 – 2.6 mmol/l

Range determined as normal for risk modelling = 2.1 - 2.6 mmol/l inclusive

CRP (C-Reactive Protein)

CRP (C-Reactive Protein) is a marker of infection or inflammation. Infection and importantly sepsis carries a significant risk of AKI. The higher the CRP the greater the severity of the infection and it would be expected the higher the risk of AKI. The relationship between CRP and AKI in this dataset (see below graph), suggests that the risk of AKI increases with a rising CRP.

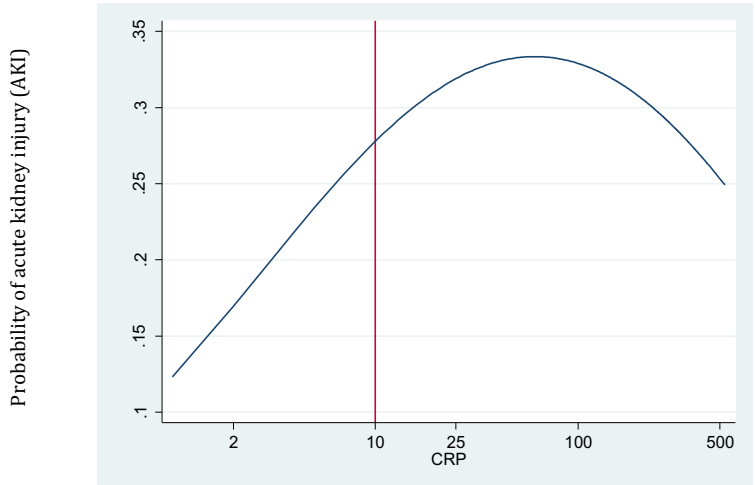


Figure 38: Relationship between c-reactive protein (CRP) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = <10 mg/l

Range determined as normal for risk modelling = ≤10 mg/l

Hb (Haemoglobin)

Hb (Haemoglobin) is the iron-containing oxygen-transport metalloprotein in red blood cells. A low Hb is a marker of acute or chronic disease and would therefore be expected to be associated with AKI. The relationship between Hb and AKI in this dataset (see below graph), suggests that both a low Hb and a high Hb have an increased risk of AKI and that risk increases the further away the value is from the normal range. The normal range of haemoglobin differs between men and women. Here is this univariable analysis no differentiation was made between men and women, however this will be accounted for in the inclusion of this variable into the multivariable analysis.

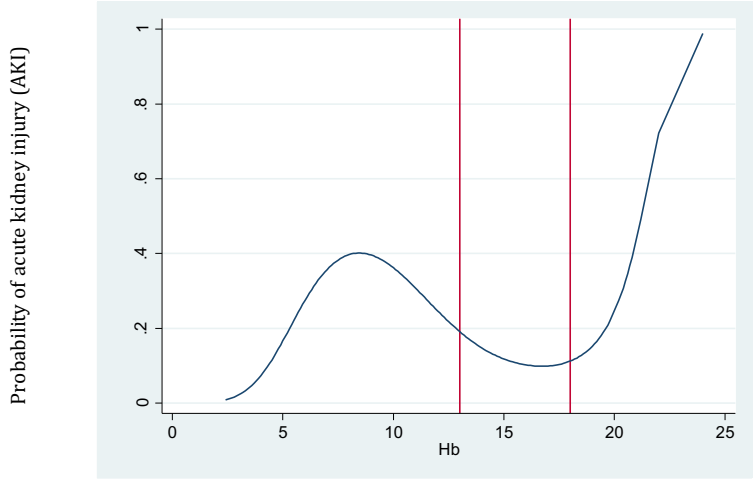


Figure 39: Relationship between haemoglobin (Hb) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 11 – 15 g/l (women)
13 – 18 g/l (men)

Range determined as normal for risk modelling = 11 - 15 g/l inclusive if female, 13 - 18 g/l inclusive if male

HbA1c (Glycated Haemoglobin)

HbA1c (Glycated Haemoglobin) gives an average of blood sugar readings over the last 120 days. A value greater than 6.5 indicates a patient with diabetes. Patients with diabetes have an increased risk of AKI. A value greater than 7.5 indicates that the diabetes is not well controlled, and it would be expected that the higher the value, the worse the diabetic control, and the higher the risk of AKI. The relationship between HbA1c and AKI in this dataset (see below graph),

suggests that having HbA1c tested (as likely defining diabetes) has an increased risk of AKI. This risk increases with rising HbA1c, up until a value of approximately 12, at which point the risk starts to fall again.

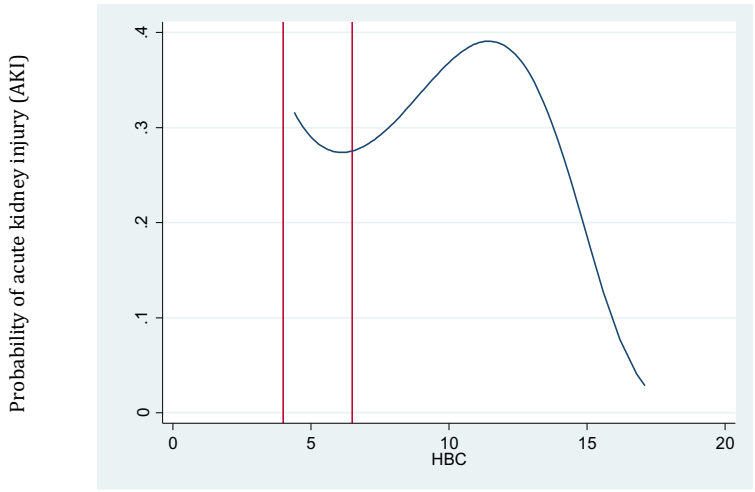


Figure 40: Relationship between glycated haemoglobin (HbA1c) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 4 – 6.5 % (Diabetes Control and Complications Trial (DCCT))*

Range determined as normal for risk modelling = ≤7.5%(DCCT)*

*The International Federation of Clinical Chemistry recommended standardisation of HbA1c following extraction of this dataset.

K (Potassium)

K (Potassium) is an electrolyte which is essential for the normal functioning of cells, importantly cardiac cells. Maintaining the gradient across the cellular membrane is essential, and changes in this can lead to cardiac arrhythmias. The K level itself in blood would not be thought to have a causal relationship with the development of AKI, however a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance. The relationship between K and AKI in this dataset (see below graph), suggests that both a low K and a high K have an increased risk of AKI and that risk increases the further away the value is from the normal range.

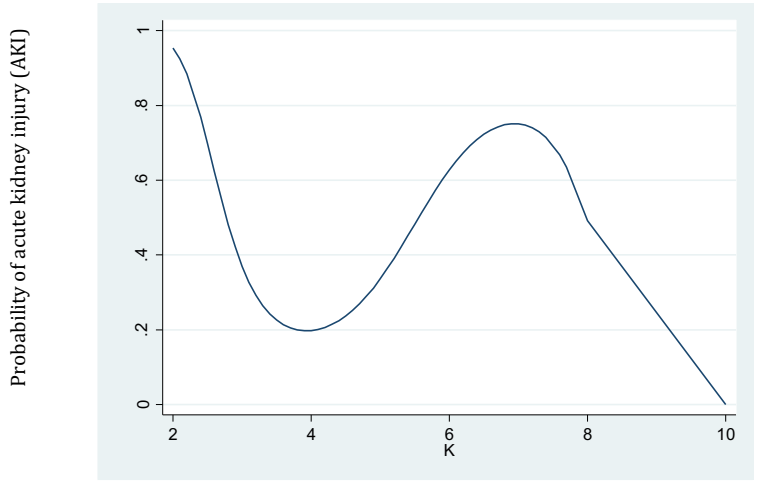


Figure 41: Relationship between potassium (K) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 3.5 – 5.3 mmol/l

Range determined as normal for risk modelling = 3.5 - 5.3 mmol/l inclusive

Mg (Magnesium)

Mg (Magnesium) is an electrolyte which is essential for the normal functioning of cells. The Mg level itself in blood would not be thought to have a causal relationship with the development of AKI, but again a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance. The relationship between Mg and AKI in this dataset (see below graph), suggests that both a low Mg and a high Mg have an increased risk of AKI and that risk increases the further away the value is from the normal range.

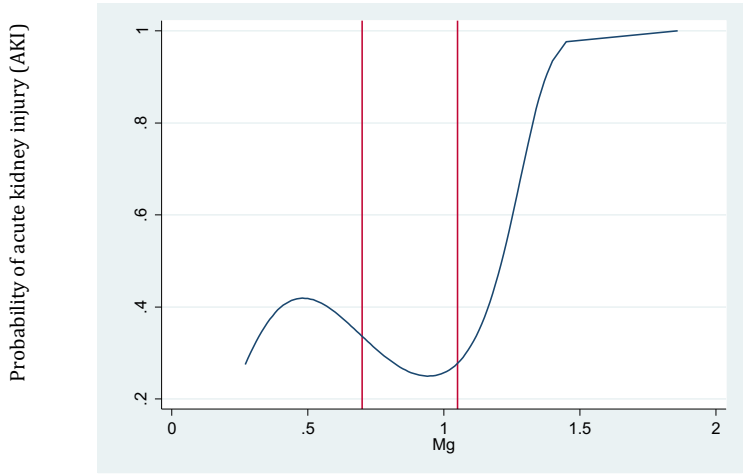


Figure 42: Relationship between magnesium (Mg) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 0.70 – 1.05 mmol/l

Range determined as normal for risk modelling = 0.7 - 1.0 mmol/l inclusive

Na (Sodium)

Na (Sodium) is an electrolyte which is essential for the normal functioning of cells. The Na level itself in blood would not be thought to have a causal relationship with the development of AKI, but again a low or high serum level may be a reflection of acute illness and changes in electrolyte and fluid balance. A low Na may also signify diuretic medication use. The relationship between Na and AKI in this dataset (see below graph), suggests that both a low Na and a high Na have an increased risk of AKI and that risk increases the further away the value is from the normal range.

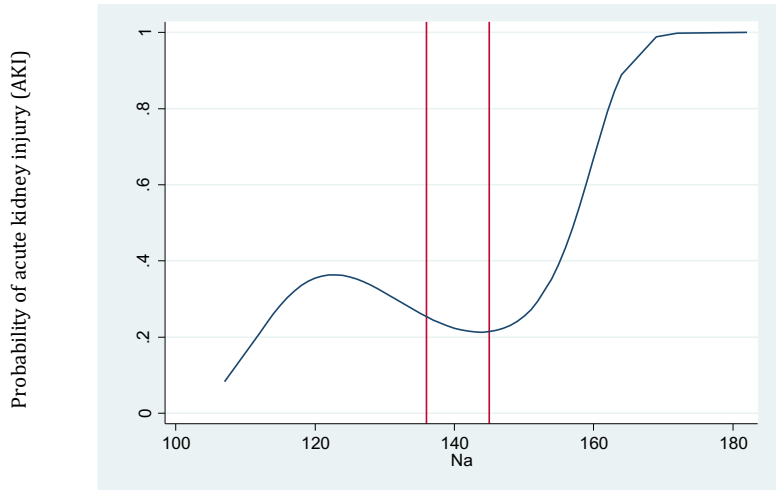


Figure 43: Relationship between sodium (Na) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 136 – 145 mmol/l

Range determined as normal for risk modelling = 136 - 145 mmol/l to inclusive

PLT (Platelets)

PLT (Platelet) count is a measure of the number of platelets in the blood. Platelets are essential for the clotting of the blood. The PLT level itself in blood would not be thought to have a causal relationship with the development of AKI. However, a low platelet count may be related to haematological disease or acute illness, and a high platelet count may also signify acute illness and specifically inflammation / infection. In both of these instances an increased risk of AKI would be expected clinically. The relationship between PLT and AKI in this dataset (see below graph), suggests that both a low PLT and a high PLT have an

increased risk of AKI and that risk increases the further away the value is from the normal range.

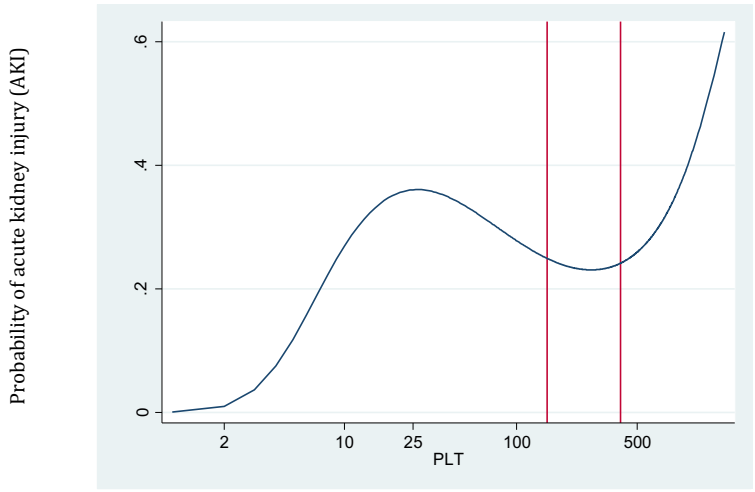


Figure 44: Relationship between platelets (PLT) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 150 – 400x10^9/l

Range determined as normal for risk modelling = 150 - 400x10^9/l inclusive

WBC (White Blood Cells)

WBC (White Blood Cells) count is a direct marker of infection. A low (<4) or high (>11) WBC can signify infection and an infection carries a risk of AKI. The relationship between WBC and AKI in this dataset (see below graph), suggests that both a low WBC and a high WBC have an increased risk of AKI and that risk increases the further away the value is from the normal range.

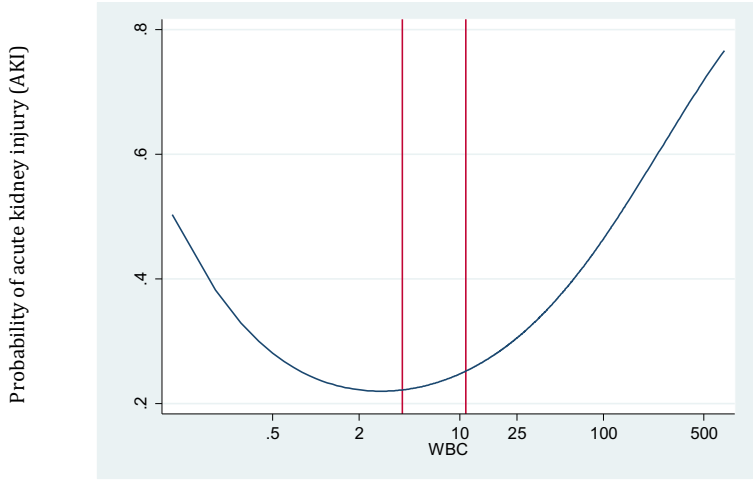


Figure 45: Relationship between white blood cell count (WBC) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 4 – 11x10^9/l

Range determined as normal for risk modelling = 1 - 11x10^9/l inclusive

CK (Creatine Kinase)

CK (Creatine Kinase) is a breakdown product of muscle. When excess muscle breakdown occurs, high levels of CK can cause damage to the kidneys and result in AKI, a condition called rhabdomyolysis. It would therefore be expected that the greater the CK the greater the risk of AKI. However, the relationship between CK and AKI in this dataset (see below graph), suggests that the fact that CK has been tested defines a patient with a higher risk of AKI, however lower levels of CK seem to be related to higher risk of AKI.

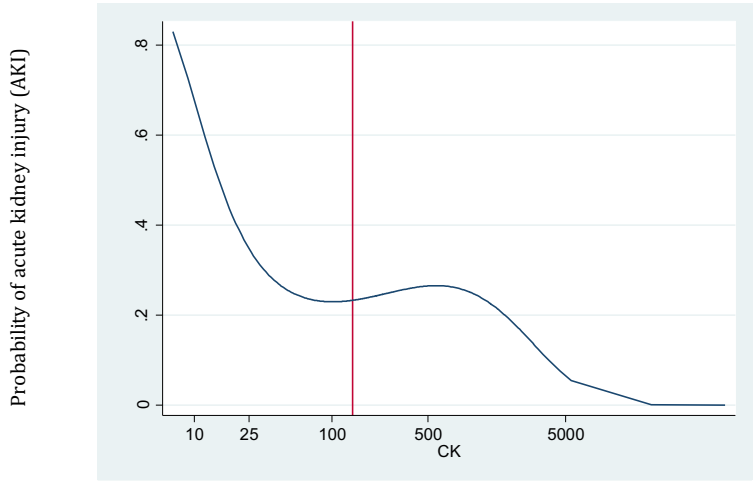


Figure 46: Relationship between creatine kinase (CK) and the probability of acute kidney injury (AKI)

Normal range (laboratory) = 0 - 142 U/l

Range determined as normal for risk modelling = ≤1000 U/l

Following the definitions of 'normal' and 'abnormal' for the pathology blood test results reported here, the next stages in modelling were to perform univariable and then multivariable analyses for each of the defined risk models (as described in the methods), using all available variables (see univariable analyses for a list of variables).

Risk Model 1: The Point of Admission to Hospital

As documented in the methods section, following the defined exclusions the full dataset was split into a 'development' and a 'validation' dataset in a 3:1 ratio.

Development

The development dataset included a total of 27,532 admissions from 20,330 patients. The outcome variable of interest in this model was the presence of acute kidney injury (AKI) on admission to hospital. In order to assess which variables in the dataset were associated with the outcome variable, initially a series of univariable ordinal logistic regression analyses were performed. The results of this univariable analysis are reported in Table 12. In this analysis the odds ratios (calculated as the exponential of the parameter estimates (beta)) are reported to demonstrate the sizes of the effects, with p-values to define the significance of each variable in terms of the outcome. This univariable analysis includes both categorical variables in which the odds ratio defines the odds of being in the next highest outcome category (for example 'AKI stage 1' compared to 'no AKI'), for each category relative to a baseline category (see Table 12) and continuous variables in which the odds ratio defines the relative change in the odds of being in the next highest outcome category for a given increase in the variable being assessed (see Table 12).

Table 12: Risk Model 1: Results of the univariable ordinal logistic regression analysis to examine variables associated with acute kidney injury (AKI) on admission

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	0.85 (0.51, 1.41)	<0.001
	Quadratic term	1.08 (0.99, 1.18)	
	Cubic term	0.996 (0.991, 1.000)	
Sex	Male	1	<0.001
	Female	0.78 (0.73, 0.84)	
Admission in last 30 days	No	1	0.002
	Yes	1.13 (1.05, 1.21)	

Admissions in last 2-12 months	0	1	<0.001
	1 - 2	1.64 (1.52, 1.77)	
	3 - 5	2.24 (2.03. 2.46)	
	6+	2.80 (2.43, 3.22)	
Outpatient attendances in last 12 months	0	1	<0.001
	1 - 2	1.10 (1.01, 1.20)	
	3 - 5	1.29 (1.17. 1.41)	
	6+	1.67 (1.52, 1.84)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.47 (1.13, 1.90)	
	Blood diseases	0.62 (0.43. 0.87)	
	Circulatory system	0.71 (0.59, 0.86)	
	Digestive system	0.66 (0.55, 0.80)	
	Diseases of the head/neck	0.19 (0.09, 0.40)	
	Genitourinary system	1.57 (1.30, 1.91)	
	Musculoskeletal	0.33 (0.26, 0.41)	
	Nervous system	0.44 (0.33, 0.60)	
	Respiratory system	1.02 (0.85, 1.23)	
	Skin	0.84 (0.65, 1.08)	
	Endocrine/metabolic	1.74 (1.47, 2.23)	
	Injury/Poisoning	0.47 (0.38, 0.57)	
	Mental disorders	0.59 (0.42, 0.83)	
	Symptoms/signs	0.44 (0.37, 0.53)	
	Other	0.35 (0.16, 0.73)	
Calcium – most recent result in	Not measured	1	<0.001

last 30 days			
	Normal (2.2 - 2.6)	1.24 (1.13, 1.36)	
	Abnormal	1.89 (1.34, 2.66)	
CRP (C-Reactive Protein) - most recent result in last 30 days	Not measured	1	<0.001
	Normal (≤10)	0.86 (0.78, 0.96)	
	Abnormal	1.49 (1.36, 1.62)	
Hb (Haemoglobin) - most recent result in last 30 days	Not measured	1	<0.001
	Normal (f: 11 - 15) (†)	0.77 (0.71, 0.84)	
	Abnormal	1.76 (1.62, 1.91)	
HbA1c (glycated haemoglobin) - 12-month average	Not measured	1	<0.001
	Normal (≤ 7.5)	1.43 (1.31, 1.56)	
	Abnormal	1.93 (1.71, 2.17)	
Potassium - most recent result in last 30 days	Not measured	1	<0.001
	Normal (3.5 - 5.3)	1.17 (1.09, 1.25)	
	Abnormal	1.79 (1.52, 2.10)	
Sodium - most recent result in last 30 days	Not measured	1	<0.001
	Normal (136 - 145)	1.11 (1.04, 1.20)	

	Abnormal	1.50 (1.36, 1.65)	
Combined sodium / potassium - most recent result in last 30 days	Not measured	1	<0.001
	Both normal	1.07 (1.00, 1.16)	
	Na only abnormal	1.44 (1.31, 1.60)	
	K only abnormal	1.66 (1.35, 2.05)	
	Both abnormal	1.96 (1.50, 2.55)	
PLT (Platelets) - most recent result in last 30 days	Not measured	1	<0.001
	Normal (150 - 400)	1.08 (1.01, 1.16)	
	Abnormal	1.44 (1.28, 1.62)	
Troponin – tested in last 12 months	0	1	<0.001
	1	2.33 (2.07, 2.62)	
	2+	3.38 (2.72, 4.19)	
WBC (White Blood Cells) - most recent result in last 30 days	Not measured	1	<0.001
	Normal (1 - 11)	1.13 (1.05, 1.21)	
	Abnormal	1.26 (1.12, 1.41)	
Blood culture – within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	1.95 (1.70, 2.22)	

	Significant	4.67 (3.61, 6.04)	
Modified Charlson Co-Morbidity Score	≤ 0	1	<0.001
	1 - 10	1.55 (1.40, 1.72)	
	11+	3.11 (2.84, 3.41)	
	Not recorded	1.04 (0.91, 1.19)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.63 (0.43, 0.94)	<0.001
	Quadratic term	0.93 (0.84, 1.03)	
	Cubic term	1.01 (1.00, 1.02)	
Drugs taken (+)	0	1	<0.001
	1	1.30 (1.18, 1.43)	
	2 or 3	1.93 (1.71, 2.18)	
	Not recorded	0.62 (0.57, 0.67)	
Faeces culture – within 2 weeks prior to admission	Not taken	1	<0.001
	Taken	1.74 (1.32, 2.30)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks	Not taken	1	<0.001

prior to admission			
	Not significant	1.20 (0.95, 1.52)	
	Significant	1.75 (1.54, 2.00)	
Proteinuria (worst result)	Not done	1	<0.001
	1	1.39 (1.27, 1.53)	
	2 or 3	2.66 (2.42, 2.91)	
Sputum culture - within 2 weeks prior to admission	Not taken	1	0.90
	Taken	1.02 (0.71, 1.48)	
Wound Swab / Fluid Aspirate culture – within 2 weeks prior to admission	Not taken	1	0.07
	Not significant	0.62 (0.39, 0.99)	
	Significant	1.14 (0.91, 1.44)	

See Appendix 7 for definitions and derivations.

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline eGFR

(†) Normal range 13-18 for males

(+) Total number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

The results reported in terms of odds ratios in Table 12 are clearly understandable for the categorical variables, however for the continuous variables the associations between these variables and the outcome variable of AKI are less clear. These associations are most effectively demonstrated graphically. The relationship between these continuous variables (age and baseline estimated glomerular filtration rate (eGFR)) and the probability of acute

kidney injury (AKI) are shown in Figures 47 (age) and 48 (eGFR) respectively. The outcome of 'any AKI' is plotted here.

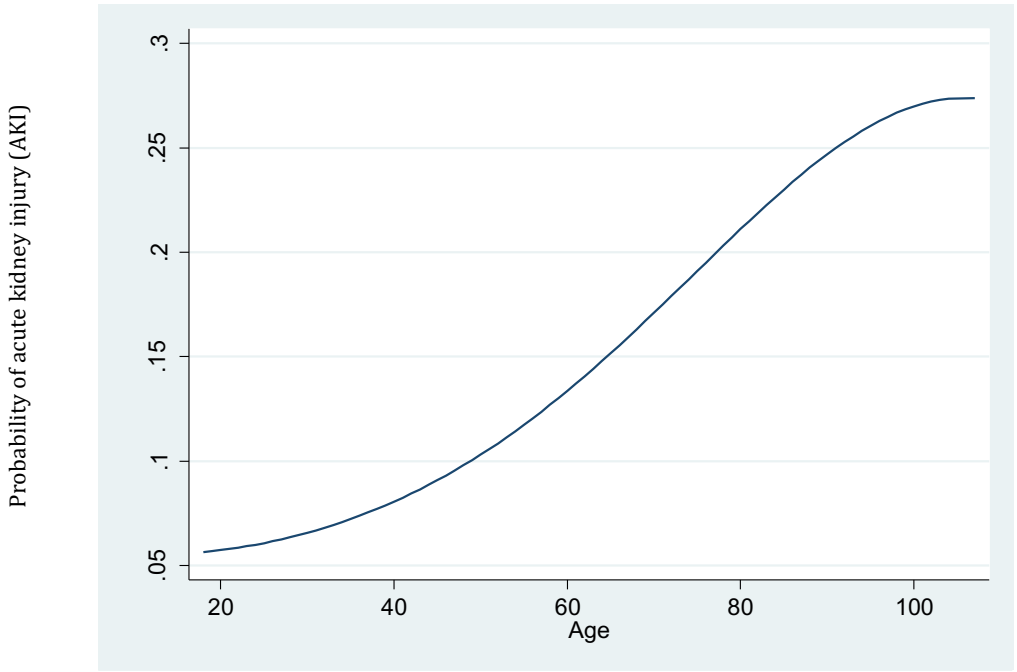


Figure 47: Risk Model 1: Relationship between age and the probability of acute kidney injury (AKI) in the univariable analysis

The probability of AKI increases with increasing age as may be expected from the literature review in Chapter 1 and the epidemiological data presented in Chapter 2.

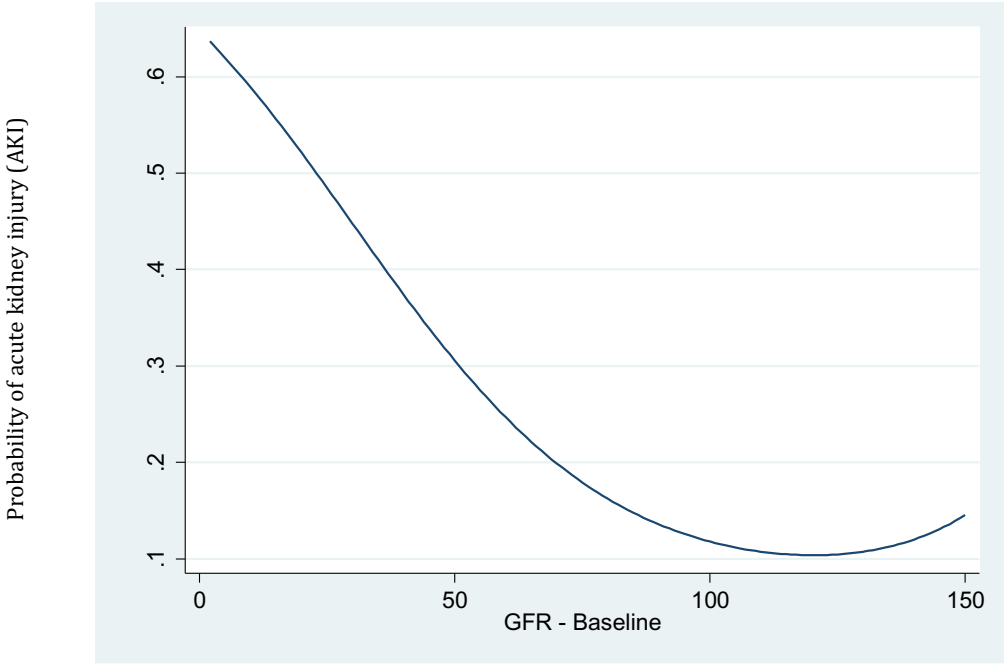


Figure 48: Risk Model 1: Relationship between baseline estimated glomerular filtration rate (eGFR) and the probability of acute kidney injury (AKI) in the univariable analysis

The probability of AKI decreases with increasing estimated glomerular filtration rate (eGFR) or on the converse this can be interpreted as the poorer or lower the kidney function, the higher the probability of AKI, which is in concordance with the epidemiological data presented in Chapter 2.

The next step in risk modelling was to perform a multivariable analysis. The first step in this multivariable analysis was to assess for collinearity. An assessment for collinearity suggested this existed between haemoglobin (Hb), white blood cell count (WBC) and platelets (PLT), and also between sodium (Na) and potassium (K). What was apparent was that these pathology blood tests were performed in the same patients. For example, a patient who had an Hb test performed also had a WBC and PLT test performed. Also, conversely, if a patient did not have an Hb test performed they would also not have a WBC or a PLT test performed. The same was true for Na and K. This clinically makes sense, as when a clinician orders an Hb test, this is ordered as part of a full blood count (FBC) which also includes WBC and PLT, along with a number of other blood count parameters not included in the modelling here. Also, for Na and K, clinically these are ordered as part of a test for renal function and electrolytes. For both of these

instances of collinearity, the 'not measured' category was therefore almost equivalent where there was collinearity.

In order to deal with this collinearity, firstly in the sub-group of patients who had all three tests of Hb, WBC and PLT performed, the association between these test results and the stage of AKI was assessed. This demonstrated that only the Hb was statistically significant with respect to the outcome of AKI, as WBC and PLT were not significant when they were corrected for Hb. The decision was therefore made to only include Hb in the multivariable analysis and remove WBC and PLT. Additionally, in the subgroup of patients who had both Na and K blood tests performed, the association between these results and the stage of AKI was assessed. In this analysis it appeared that both tests were independently associated with the outcome variable of AKI. The decision was therefore made to derive a combined variable of the following categories: 'not measured' (one or both tests), 'both normal', 'Na only abnormal', 'K only abnormal' and 'both tests abnormal'.

To determine the final model, a backwards selection method was employed which retained only the statistically significant variables (in relation to the outcome variable of AKI). This resulted in the removal, in the following order of the variables: wound swab/fluid aspirate culture, combined sodium/potassium, calcium, gender, faeces culture, sputum culture, and number of outpatient attendances in the last 12 months.

It is likely that the culture variables were removed from the analysis in backwards selection as they are defining the presence of infection and in this case the c-reactive protein (CRP) is a better predictor of this as it provides both detection of infection but also the degree of severity (which along with this one would expect the risk of AKI), with the higher the CRP the more severe the infection and the greater the risk of AKI. The outpatient attendances in 12 months likely fell out of the model as this is a marker of co-morbidity. The greater the co-morbidity the patient has (and with this the greater the risk of

AKI), the more likely they are to have outpatient attendances in respect of these co-morbidity. Therefore the co-morbidity score is likely to be a better predictor.

The final regression model is reported in Table 13.

Table 13: Risk Model 1: Results of the multivariable ordinal logistic regression analysis to examine variables associated with acute kidney injury (AKI) on admission

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	3.35 (1.82, 6.16)	<0.001
	Quadratic term	0.89 (0.81, 0.98)	
	Cubic term	1.003 (0.998, 1.009)	
Admission in last 30 days	No	1	<0.001
	Yes	0.82 (0.74, 0.91)	
Admissions in last 2-12m	0	1	<0.001
	1 - 2	1.28 (1.16, 1.42)	
	3 - 5	1.54 (1.36. 1.75)	
	6+	2.01 (1.70, 3.80)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.37 (1.05, 1.80)	
	Blood diseases	0.50 (0.35. 0.72)	
	Circulatory system	0.66 (0.55, 0.80)	
	Digestive system	0.83 (0.68, 1.02)	
	Diseases head/neck	0.30 (0.15, 0.63)	
	Genitourinary system	1.76 (1.43, 2.15)	
	Musculoskeletal	0.39 (0.30, 0.49)	
	Nervous system	0.53 (0.39, 0.72)	
	Respiratory system	0.90 (0.75, 1.09)	

	Skin	0.87 (0.68, 1.16)	
	Endocrine/metabolic	1.64 (1.26, 2.13)	
	Injury/Poisoning	0.55 (0.45, 0.67)	
	Mental disorders	0.79 (0.55, 1.12)	
	Symptoms/signs	0.53 (0.44, 0.64)	
	Other	0.36 (0.16, 0.79)	
CRP (C-Reactive protein) - most recent result in last 30 days	Not measured	1	0.009
	Normal (≤10)	0.99 (0.86, 1.14)	
	Abnormal	1.19 (1.04, 1.35)	
Hb (Haemoglobin) - most recent result in last 30 days	Not measured	1	<0.001
	Normal (f: 11 - 15) (†)	0.79 (0.70, 0.89)	
	Abnormal	1.10 (0.98, 1.24)	
HbA1c (glycated haemoglobin) - 12-month average	Not measured	1	0.008
	Normal (≤ 7.5)	1.06 (0.96, 1.17)	
	Abnormal	1.24 (1.08, 1.43)	
Troponin – tested in last 12 months	0	1	<0.001
	1	1.27 (1.11, 1.45)	
	2+	1.46 (1.15, 1.85)	
Blood culture – within 2 weeks	Not taken	1	<0.001

prior to admission			
	Not significant	1.49 (1.29, 1.73)	
	Significant	3.12 (2.36, 4.12)	
Modified Charlson Co-Morbidity Score	≤ 0	1	<0.001
	1 - 10	1.08 (0.97, 1.21)	
	11+	1.37 (1.23, 1.53)	
	Not recorded	1.11 (0.96, 1.29)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.93 (0.60, 1.43)	<0.001
	Quadratic term	0.83 (0.74, 0.93)	
	Cubic term	1.03 (1.02, 1.04)	
Drugs taken (+)	0	1	<0.001
	1	1.15 (1.04, 1.27)	
	2 or 3	1.38 (1.20, 1.58)	
	Not recorded	0.86 (0.77, 0.95)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	1.05 (0.80, 1.36)	
	Significant	1.37 (1.19, 1.59)	

Proteinuria (worst result)	Not done 1 2 or 3	1 1.07 (0.96, 1.19) 1.38 (1.23, 1.54)	<0.001

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline GFR

(†) Normal range 13-18 for males

(+) Total number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

In this multivariable analysis, as would be expected following adjustment for other variables in the model, the effect of each variable on the outcome variable of acute kidney injury (AKI) was reduced, however the effects were similar to those demonstrated in the univariable analyses. An exception to this in the model was the variable 'admission in the last 30 days' (this variable documents/describes whether the patient had been previously admitted to hospital in the 30 days prior to date of admission for the current admission being considered). In the univariable analysis the odds ratio for 'admission in the last 30 days' was 1.13 if admitted in the last 30 days compared to those patients who were not. This suggests an increased risk of a higher stage of AKI in patients who had been admitted in the previous 30 days in comparison to those who had not. However, in the multivariable analysis the odds ratio for patients who had been admitted in the previous 30 days was 0.82, suggesting the opposite effect, a lower AKI stage in these patients.

As with the univariable analyses the continuous variables, age and baseline estimated glomerular filtration rate (eGFR), are difficult to interpret from the odds ratios. To demonstrate the relationship between these continuous variables and the outcome variable of acute kidney injury (AKI), 'average' values for the other variables in the model were assumed. Figure 49 plots age against the adjusted predicted probability of AKI and Figure 50 plots estimated glomerular filtration rate (eGFR) against the adjusted predicted probability or AKI.

As in the univariable analysis, increasing age is associated with an increased risk of AKI, however, in the multivariable analysis this risk peaks around the age of 75. However, for baseline estimated glomerular filtration rate (eGFR) after adjusting for other variables in the model, there appears to be an increased probability of AKI in patients with both a lower than normal (assuming a normal eGFR of 60-120) and a higher than normal eGFR (kidney function) (Figure 50).

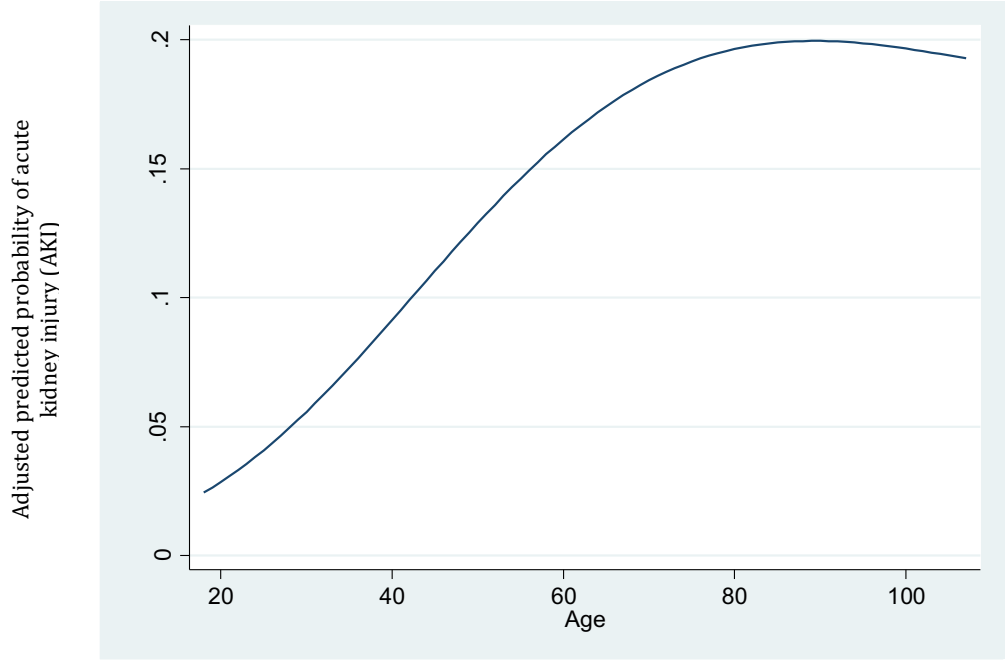


Figure 49: Risk Model 1: Relationship between age and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis

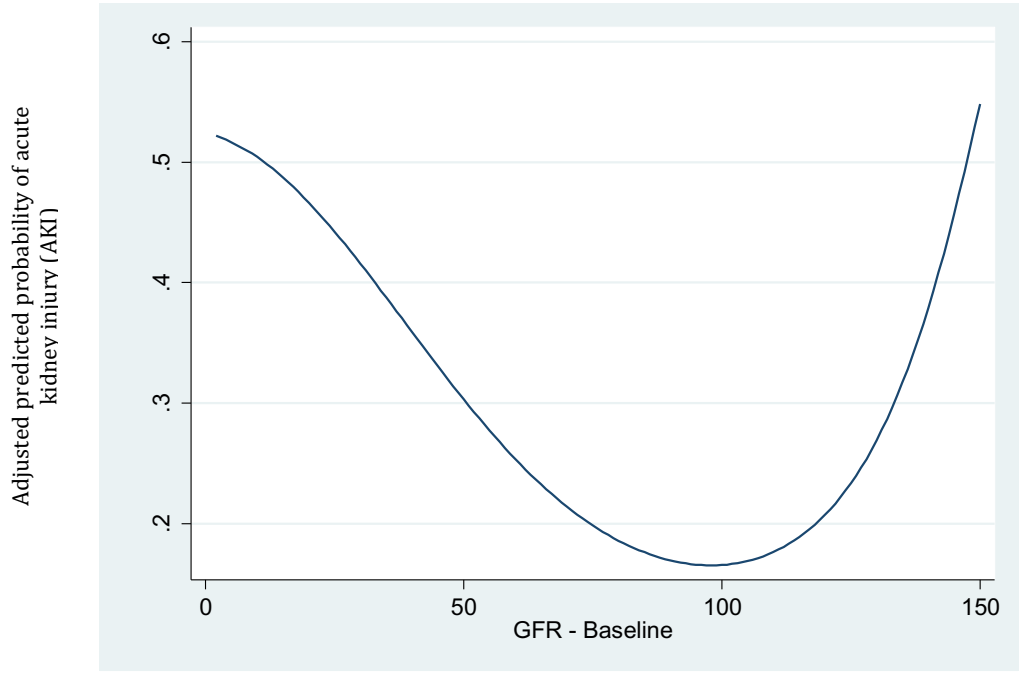


Figure 50: Risk Model 1: Relationship between estimated glomerular filtration (eGFR) and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis

Validation

As described, 25% of the final dataset was used for validation of the developed risk model. The validation dataset consisted of 9,177 patient hospital admissions/episodes. Of those, 20 admissions were removed due to missing data leaving a final validation dataset of 9,157 admissions. Comparison between the validation and development datasets demonstrated good matching, which would be expected following random selection method.

To firstly assess validity, the patient hospital admissions/episodes were separated into risk groups based on the predicted probability of AKI. This was performed in two analyses, firstly, for the probability of any AKI as the outcome, with the risk groups as ≤10%, 10-20%, 20-40% and >40% and secondly, for the probability of either AKI stage 2 or 3 in which the risk groups were ≤2%, 2-5%, 5-10%, ≥10% (see Table 14). For each of the risk groups in the two analyses, the 'expected' risk was calculated based on predicted probabilities, and compared to the observed occurrence. The results of these analyses are reported in Table 14

and demonstrate a good discrimination between risk groups for both analyses (outcome of 'any AKI' and 'AKI stage 2 or 3').

Table 14: Risk Model 1: Comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for AKI on admission

Outcome Categorisation	Risk group	N	Mean Expected %	Observed %
Any AKI	≤ 10%	3325	6.2%	5.0%
	10% - 20%	3057	14.3%	14.8%
	20% - 40%	2178	27.5%	28.4%
	> 40%	597	51.7%	51.6%
AKI Stage 2 or 3	≤ 2%	3962	1.2%	0.8%
	2% - 5%	3358	3.2%	3.8%
	5% - 10%	1294	6.9%	7.2%
	> 10%	543	15.8%	11.4%

In both analyses the observed percentages fell within the boundaries of the risk groups, suggesting good calibration. Table 14 also demonstrates a good agreement between the predicted/expected percentages and those that were observed by the data, with a slight exception in the second analysis (outcome of 'AKI stage 2 or 3'), where the observed percentage of patient admissions in the high-risk group (>10%) was less than that predicted by the model. Following this, based on the predicted probabilities, Receiver Operating Characteristic (ROC) curves were plotted and the Area Under the Receiver Operating Characteristic (AUROC) curves calculated, for both 'any AKI' and 'AKI stage 2 or 3' as outcomes. The ROC curve for 'any AKI' is demonstrated in Figure 51 and for 'AKI stage 2 or 3' in Figure 52. The AUROC values for both 'any AKI' and 'AKI stage 2 or 3' are reported in Table 15.

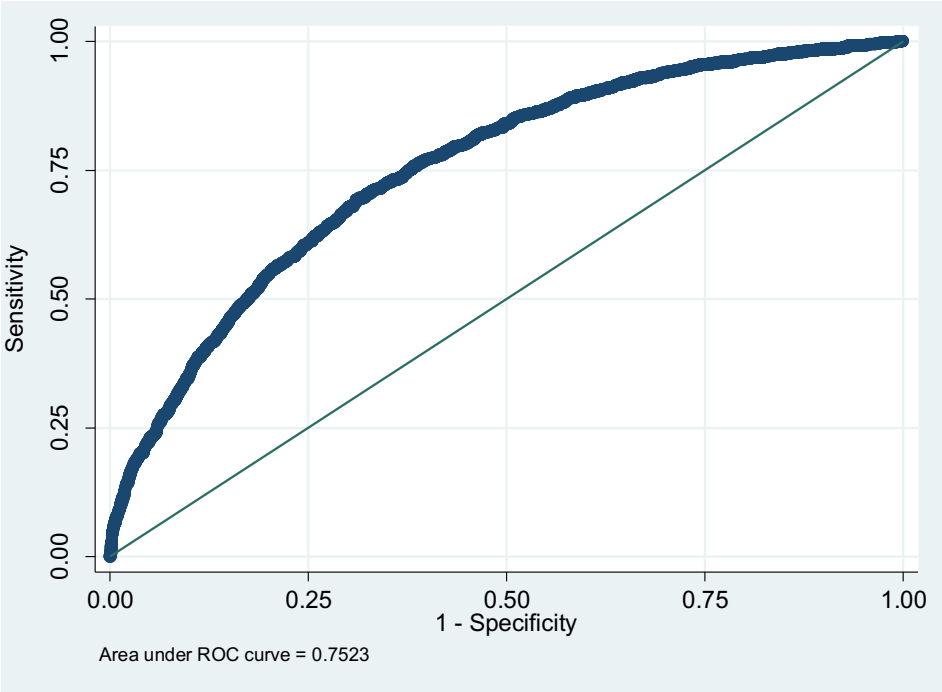


Figure 51: Risk Model 1: Receiver Operating Characteristic (ROC) curve for the prediction of 'any AKI'

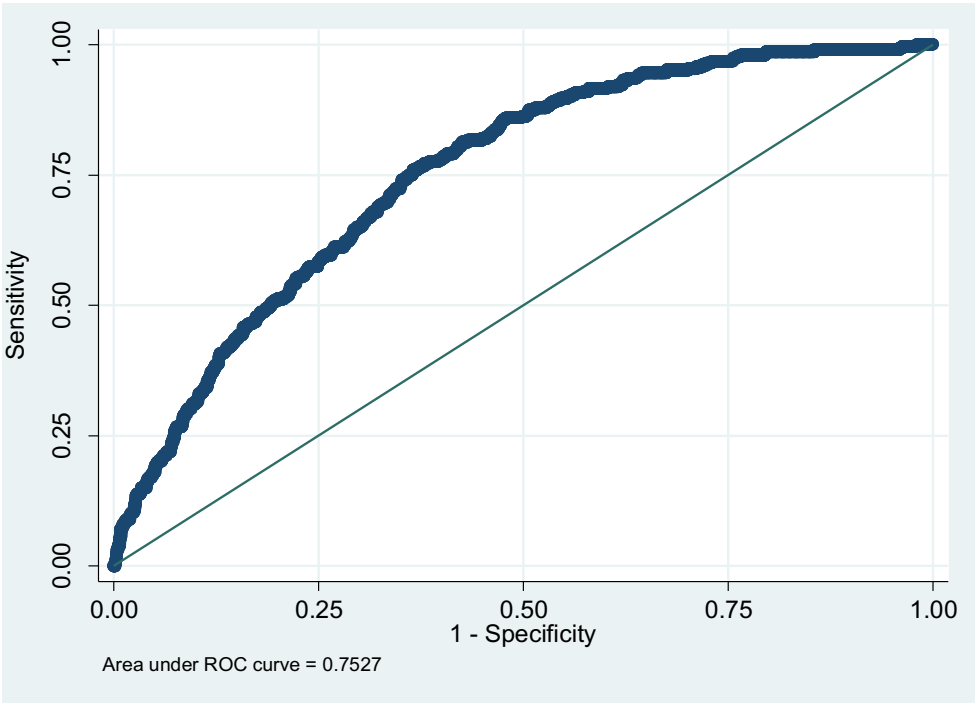


Figure 52: Risk Model 1: Receiver Operating Characteristic (ROC) Curve for the prediction of 'AKI stage 2 or 3'

Table 15: Risk Model 1: The Receiver Operating Characteristic (ROC) analyses for validation

Outcome	AUROC (95% CI)	Interpretation

Categorisation		
Any AKI **AKI Stage 2 or 3**	0.75 (0.74, 0.77) 0.75 (0.73, 0.78)	Fair Fair

An AUROC of 0.75 would suggest fair discriminatory power of risk Model 1 (predicting AKI on admission) being validated here.

Finally, a Hosmer-Lemeshow test was performed to compare the numbers of patients/ admissions experiencing AKI predicted by the model, and those observed in the data, for each risk group in turn. The results of this analysis are reported in the Table 16.

Table 16: Risk Model 1: A comparison of the observed numbers of AKI in each AKI group and the numbers predicted by the model using the Hosmer-Lemeshow test for validation

Outcome Categorisation	Risk Group	No AKI (†) Observed N (Expected N)	AKI (†) Observed N (Expected N)	$\chi 2$ statistic (*)	P-value
Any AKI	≤ 10% 10% - 20% 20% - 40% > 40%	3158 (3119) 2606 (2619) 1559 (1580) 289 (289)	167 (206) 451 (438) 619 (598) 308 (308)	9.4	0.009
AKI Stage 2 or 3	≤ 2% 2% - 5% 5% - 10% > 10%	3931 (3916) 3232 (3250) 1201 (1205) 481 (457)	31 (46) 126 (108) 93 (89) 62 (86)	16.4	0.0003

(*) With 2 degrees of freedom

(†) Or AKI stage 2 or 3 for second outcome categorisation

This test suggests a lack of fit both for the prediction of the outcome 'any AKI' and also, and slightly more so, for 'AKI stage 2 or 3' as evidenced by a statistically significant difference between the numbers predicted by the model and those observed in the data. The Hosmer-Lemeshow test is however sensitive to slight differences between predicted and observed frequencies. As in the first validation analysis (Table 14), there is an over-prediction by the model of patients/admissions in the highest risk group (>10%) for the outcome of 'AKI stage 2 or 3'. For the outcome 'any AKI', the prediction of the model is good in the highest risk group (>40%), however, in the lowest risk group (≤10%) the model over-predicts (Table 16).

Validation in a second population

As described in the methods the calibration and discriminative ability of risk Model 1 (predicting AKI on admission) was then assessed in the Medway (patients presenting to Medway NHS Foundation Trust) population to provide validation in a second demographically different population. Following exclusions (as in the EKHUFT dataset) the Medway dataset included 4,726 patient hospital admissions. For each admission the predicted probability of AKI was determined from the risk model. In comparison of the EKHUFT and Medway datasets, there were differences as would be expected (hence choice of Medway as a second validation population) in terms of demographics and also of occurrence of AKI. AKI was experienced in 17% of patient hospital admissions in the EKHUFT dataset in comparison to 23% in the Medway dataset. As with validation in the EKHUFT dataset, the patient hospital admissions/episodes were separated into the same risk groups based on the predicted probability of AKI, for both the outcomes 'any AKI' and 'AKI stage 2 or 3'. Again, the 'expected' risk was calculated based on predicted probabilities and compared to the observed occurrence in the data.

Table 17: Risk Model 1: Comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for AKI on admission in the second population (Medway)

Outcome Categorisation	Risk Group	N	Mean Expected %	Observed %
Any AKI	≤ 10%	1961	6.1%	10.7%
	10% - 20%	1597	14.1%	23.0%
	20% - 40%	960	27.1%	39.8%
	> 40%	208	51.1%	63.0%
AKI Stage 2 or 3	≤ 2%	2329	1.1%	2.1%
	2% - 5%	1657	3.2%	5.9%
	5% - 10%	552	6.8%	9.6%
	> 10%	188	15.3%	18.6%

Table 17 summarises these results and suggests good discrimination between risk groups for both the outcome 'any AKI' and 'AKI stage 2 or 3', however, the calibration appears less good in this population. In each of the risk groups the expected/predicted percentage was lower than that observed in the data, and in some cases the observed percentage lay outside of the range of the risk category (Table 17).

Again, discrimination by risk Model 1 was assessed in the second population of Medway by plotting ROC curves (Figures 53 ('any AKI') and 54 ('AKI stage 2 or 3')), and calculating the AUROC (Table 18) for both the outcomes of 'any AKI' and 'AKI stage 2 or 3'.

These results demonstrate fair discriminatory power of risk Model 1 in the second population, although slightly poorer than that observed for the internal validation in the EKHUFT dataset (0.72 (Medway) in comparison to 0.75 (EKHUFT internal validation)).

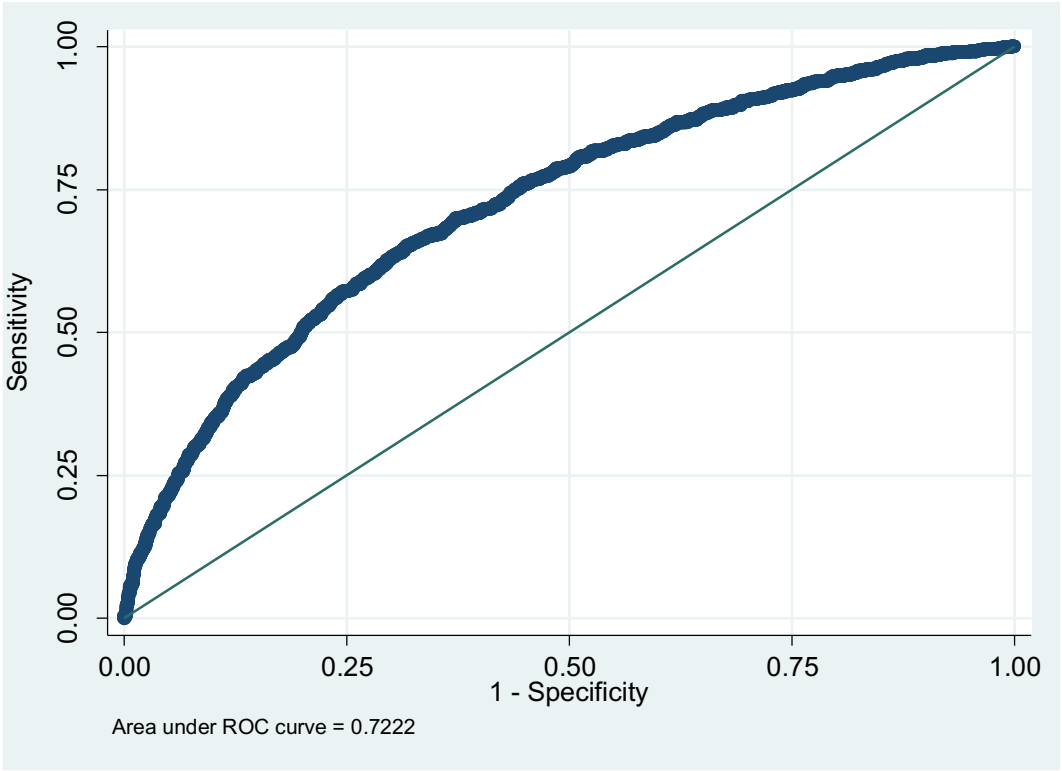


Figure 53: Risk Model 1: Receiver Operating Characteristic (ROC) Curve for the prediction of 'any AKI' in the second population

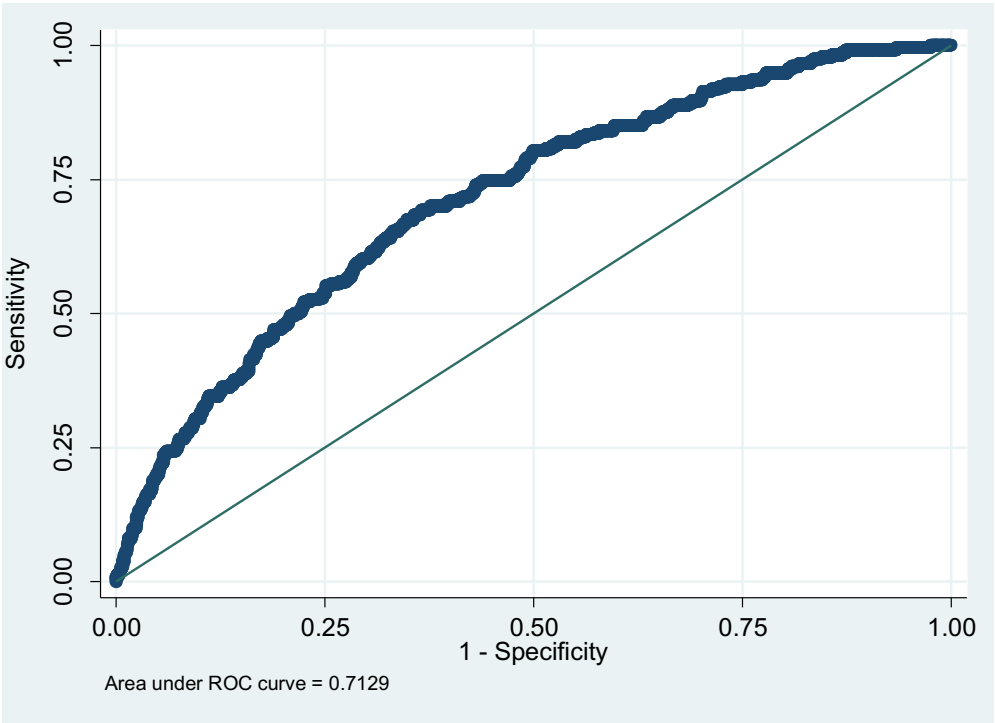


Figure 54: Risk Model 1: Receiver Operating Characteristic (ROC) Curve for the prediction of 'AKI stage 2 or 3' in the second population

Table 18: Risk Model 1: The Receiver Operating Characteristic (ROC) analyses in the second population (Medway) for validation

Outcome Categorisation	**AUROC (95% CI)**	**Interpretation**
Any AKI	0.72 (0.71, 0.74)	Fair
AKI Stage 2 / 3	0.71 (0.68, 0.75)	Fair

Finally, the Hosmer-Lemeshow test was performed in this second population (Medway), as in the internal validation (EKHUFT). The results are reported in Table 19 and suggest a lack of fit of the models to the second population validation dataset.

Table 19: Risk Model 1: A comparison of the observed numbers of AKI in each AKI group and the numbers predicted by the model in the second population using the Hosmer-Lemeshow test for validation

Outcome Categorisation	**Risk Group**	**No AKI (†) Observed N (Expected N)**	**AKI (†) Observed N (Expected N)**	**$\chi 2$ statistic (*)**	**P-value**
Any AKI	≤ 10%	1752 (1842)	209 (119)	269.6	<0.0001
	10% - 20%	1229 (1372)	368 (225)		
	20% - 40%	578 (700)	382 (260)		
	> 40%	77 (119)	131 (106)		
AKI Stage 2 or 3	≤ 2%	2280 (2302)	49 (27)	66.9	<0.0001
	2% - 5%	1560 (1604)	97 (52)		
	5% - 10%	499 (515)	53 (37)		
	> 10%	153 (159)	35 (29)		

(*) With 2 degrees of freedom

(†) Or AKI stage 2 or 3 for second categorisation

As previously demonstrated in comparison of expected and observed probabilities (Table 17), the Hosmer-Lemeshow test again demonstrates that the number of admissions with AKI for each risk group is significantly higher than that expected/predicted by the model (Table 19).

Summary

The results for risk Model 1 (predicting AKI on admission) reported here suggest that this model has fair discriminatory power and is able to separate high from low risk patients for the outcome of 'any AKI' or the more severe 'AKI stage 2 or 3', both in the primary EKHUFT population and the second demographically different population (Medway).

In terms of area under the receiver operating characteristic curve (AUROC) the model produces values of 0.75 ('any AKI') in the primary population and 0.72 ('any AKI') in the secondary population. The calibration of the model is good in the primary (EKHUFT) population with good agreement of expected/predicted AKI and that observed in the data. This is less so on validation in the second population in which risk Model 1 under-predicts the risk of AKI both in the analysis with 'any AKI' as the outcome and with 'AKI stage 2 or 3' as the outcome. This may be partly explained by the higher occurrence of both 'any AKI' and 'AKI stage 2 or 3' in the second population of Medway.

Risk Model 2: Predicting New AKI at 72 Hours

As documented in the methods section, following the defined exclusions the full dataset was split into a 'development' and a 'validation' dataset in a 3:1 ratio.

Development

The development dataset included a total of 7,556 admissions from 6,626 patients. The outcome variable of interest in this model was the presence of new acute kidney injury (AKI) at 72 hours into hospital admission. In order to assess which variables in the dataset were associated with the outcome variable,

initially a series of univariable ordinal logistic regression analyses were performed. The results of this univariable analysis are reported in Table 20. In this analysis the odds ratios (calculated as the exponential of the parameter estimates (beta)) are reported to demonstrate the sizes of the effects, with p-values to define the significance of each variable in terms of the outcome. This univariable analysis includes both categorical variables in which the odds ratio defines the odds of being in the next highest outcome category (for example 'AKI stage 1' compared to 'no AKI'), for each category relative to a baseline category (see Table 20) and continuous variables in which the odds ratio defines the relative change in the odds of being in the next highest outcome category for a given increase in the variable being assessed (see Table 20).

Table 20: Risk Model 2: Results of the univariable ordinal logistic regression analysis to examine variables associated with new acute kidney injury (AKI) at 72 hours

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	1.28 (1.21, 1.35)	<0.001
Sex	Male	1	0.27
	Female	0.91 (0.78, 1.07)	
Admission in last 30 days	No	1	0.56
	Yes	0.95 (0.79, 1.14)	
Admission in last 2-12 months	0	1	<0.001
	1 - 2	1.31 (1.09, 1.58)	
	3 - 5	1.55 (1.22. 1.97)	
	6+	1.88 (1.37, 2.58)	
Outpatient attendances	0	1	0.07

in last 12 months	1 - 2	1.03 (0.84, 1.28)	
	3 - 5	1.25 (1.00. 1.55)	
	6+	1.28 (1.02, 1.62)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.80 (1.08, 3.00)	
	Blood diseases	0.63 (0.28. 1.43)	
	Circulatory system	1.09 (0.73, 1.62)	
	Digestive system	0.71 (0.47, 1.08)	
	Genitourinary system	1.54 (0.98, 2.42)	
	Musculoskeletal	0.74 (0.37, 1.47)	
	Nervous system	0.53 (0.23, 1.22)	
	Respiratory system	0.78 (0.52, 1.19)	
	Skin	0.89 (0.47, 1.69)	
	Endocrine/metabolic	0.70 (0.34, 1.43)	
	Injury/Poisoning	0.97 (0.64, 1.48)	
	Mental disorders	0.14 (0.02, 1.04)	
	Symptoms/signs	0.72 (0.46, 1.14)	
	Other	1.02 (0.29, 3.65)	
ALT (Alanine Transaminase) – most recent result in last 30 days	Not measured	1	0.84
	Normal (≤50)	1.06 (0.86, 1.32)	
	Abnormal	1.08 (0.79, 1.48)	
AMY (Amylase) – most recent result in last 30 days	Not measured	1	0.55
	Normal (≤125)	0.90 (0.73, 1.10)	
	Abnormal	1.05 (0.62, 1.79)	

BNP (Brain Natriuretic Peptide) – most recent result in last 30 days	Not measured	1	0.49
	Measured	1.19 (0.73, 1.96)	
Calcium – most recent result in last 30 days	Not measured	1	0.45
	Normal (2.2 - 2.6)	1.09 (0.92, 1.30)	
	Abnormal	1.24 (0.75, 2.03)	
CRP (C-Reactive Protein) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (≤10)	0.81 (0.59, 1.10)	
	Abnormal	1.16 (0.87, 1.53)	
Hb (Haemoglobin) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (f: 11 - 15) (†)	0.65 (0.41, 1.01)	
	Abnormal	0.94 (0.60, 1.47)	
HbA1c (glycated haemoglobin) - 12-month average	Not measured	1	<0.001
	Normal (≤ 7.5)	1.51 (1.24, 1.85)	
	Abnormal	1.52 (1.13, 2.02)	
K (Potassium) – most recent result in last 30 days	Not measured	1	0.003
	Normal (3.5 - 5.3)	0.67 (0.50, 0.91)	
	Abnormal	0.94 (0.65, 1.37)	

Mg (Magnesium) – most recent result in last 30 days	Not measured	1	0.008
	Normal (0.7 - 1.0)	0.87 (0.66, 1.15)	
	Abnormal	1.72 (1.19, 2.48)	
Na (Sodium) – most recent result in last 30 days	Not measured / Normal (136 - 145)	1	0.46
	Abnormal	1.06 (0.90, 1.25)	
PLT (Platelets) – most recent result in last 30 days	Not measured / Normal (150 – 400)	1	0.10
	Abnormal	1.17 (0.97, 1.41)	
Troponin – tested in last 12 months	0	1	<0.001
	1	1.35 (1.10, 1.66)	
	2+	2.33 (1.86, 2.93)	
WBC (White blood Cells) - most recent result in last 30 days	Not measured / Normal (1 – 11)	1	0.03
	Abnormal	1.20 (1.02, 1.40)	
CK. (Creatine Kinase) - most recent result in last 30 days	Not measured	1	0.67
	Normal ((≤ 1000)	0.96 (0.63, 1.47)	
	Abnormal	1.35 (0.68, 2.67)	
Blood culture – on	Not taken	1	0.02

admission	Taken	1.28 (1.03, 1.59)	
Modified Charlson Co-Morbidity Score	≤ 0	1	<0.001
	1 - 10	1.45 (1.12, 1.87)	
	11+	2.33 (1.86, 2.93)	
	Not recorded	1.39 (1.03, 1.88)	
Number of contrast radiology scans	0	1	0.82
	1+	1.03 (0.78, 1.37)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.54 (0.40, 0.74)	<0.001
	Quadratic term	1.03 (1.00, 1.08)	
Drugs taken (+)	0	1	<0.001
	1	1.25 (1.00, 1.58)	
	2 or 3	1.92 (1.42, 2.59)	
	Not recorded	0.85 (0.71, 1.03)	
Faeces Culture – within 2 weeks prior to admission	Not taken	1	0.30
	Taken	1.36 (0.76, 2.43)	
Faeces Culture – on admission	Not taken	1	0.42
	Taken	0.78 (0.43, 1.42)	
Mid-stream specimen	Not taken	1	0.07

of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks prior to admission			
	Not significant	0.63 (0.29, 1.36)	
	Significant	1.40 (1.00, 1.96)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – on admission	Not taken	1	0.001
	Taken	1.43 (1.15, 1.78)	
Operative Severity Score at 12 hours	0	1	0.13
	Score 1-2	0.99 (0.68, 1.44)	
	Score 3-4	1.47 (1.01, 2.13)	
Proteinuria (worst result)	Not done	1	<0.001
	1	1.27 (1.01, 1.60)	
	2 or 3	2.56 (2.08, 3.15)	
Sputum Culture – within 2 weeks prior to admission	Not taken	1	0.73
	Taken	1.14 (0.54, 2.42)	
Sputum Culture – on admission	Not taken	1	0.12
	Taken	0.54 (0.24, 1.17)	

Wound Swab / Fluid Aspirate Culture - within 2 weeks prior to admission	Not taken	1	0.42
	Taken	0.81 (0.48, 1.36)	
Wound Swab / Fluid Aspirate Culture - on admission	Not taken	1	0.55
	Taken	1.11 (0.80, 1.53)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline GFR

(†) Normal range 13-18 for males

(+) Total Number of the following drugs taken: angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

The results reported in terms of odds ratios in Table 20 are clearly understandable for the categorical variables, however for the continuous variables the associations between these variables and the outcome variable of AKI are less clear. These associations are most effectively demonstrated graphically. The relationship between these continuous variables (age and baseline estimated glomerular filtration rate (eGFR)) and the probability of acute kidney injury (AKI) are shown in Figures 55 (age) and 56 (eGFR) respectively. The outcome of 'any AKI' is plotted here.

A linear term was sufficient for age, with a ten-year increase in age associated with a 28% increase in the odds of AKI being in the next highest category / stage. A quadratic (squared) term was required for baseline eGFR.

In some cases the results reported here may seem counter intuitive where the confidence intervals(CIs) of the odds ratios cross 1, however the differences between the categories remain statistically significant. An example is for 'Hb (Haemoglobin) - most recent result in last 30 days' which has the categories: 'Not Measured', 'Normal' and 'Abnormal', with odds ratios (95% CI) of 1, 0.65 (0.41, 1.01) and 0.94 (0.60, 1.47) respectively. This occurrence is related to

relative prevalence of the categories. As the 'Not Measured' category (used as the reference / baseline for the odds ratios) is the smallest category (as the majority of hospital inpatients have a haemoglobin checked), this produces more uncertainty in the odds ratios for the outcome and hence wider CIs. If a different reference / baseline had been chosen, with larger numbers, then the odds ratios for this comparison may not cross 1.

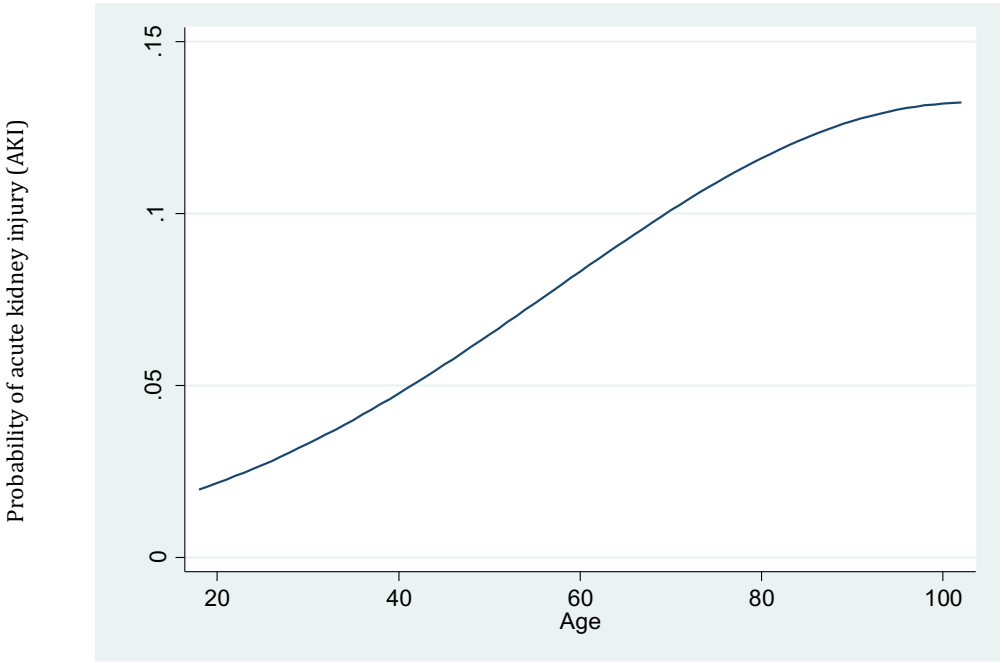


Figure 55: Risk Model 2: Relationship between age and the probability of acute kidney injury (AKI) in the univariable analysis

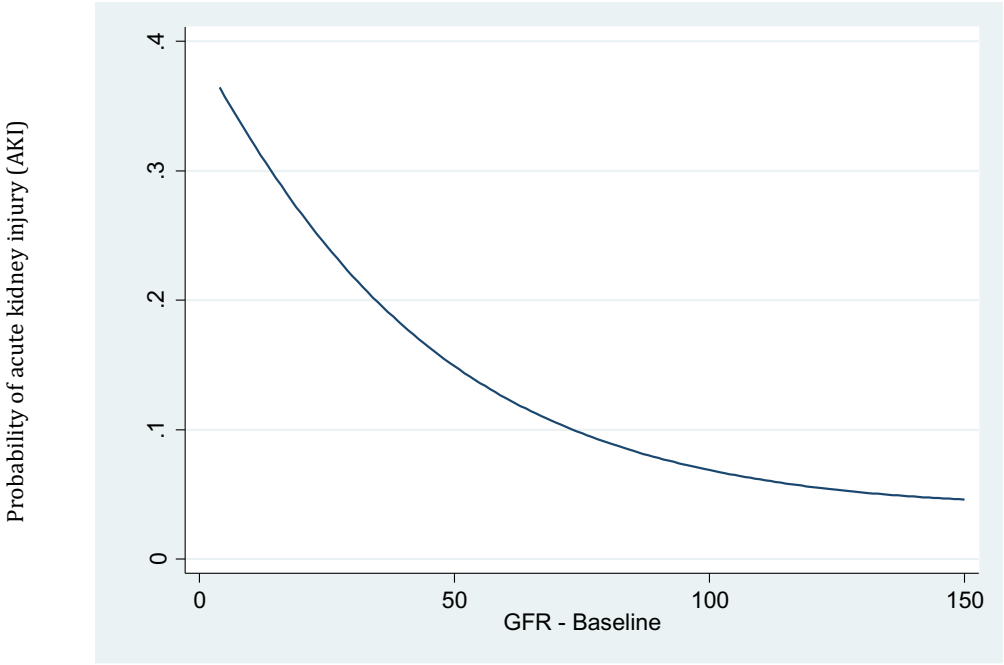


Figure 56: Risk Model 2: Relationship between baseline estimated glomerular filtration rate (eGFR) and probability of acute kidney injury (AKI) in the univariable analysis

The next step in risk modelling was to perform a multivariable analysis. The first step in this multivariable analysis was to assess for collinearity, and in this analysis there was no strong evidence of collinearity between predictors, and hence all predictors could be considered as independent variables in the multivariable analysis.

From the univariable analyses it was evident that in patients who had HbA1c tested, whether the results of the test were normal or abnormal, their risks of AKI were almost equivalent. Therefore, the decision was made to re-categorise this variable as 'not measured' or 'measured'. Clinically the assumption could be made that having HbA1c tested is a marker of having diabetes, and hence HbA1c 'not measured' could be understood as a patient not having diabetes, and 'measured' as having diabetes.

To determine the final model, a backwards selection method was employed which retained only the statistically significant variables (in relation to the outcome variable of AKI at 72 hours). This resulted in the removal, in the

following order of the variables: calcium, gender, BNP (Brain Natriuretic Peptide), CK (Creatine Kinase), outpatient attendances in 12 months, sputum culture within 2 weeks prior to admission, number of contrast radiology scans, wound swab / fluid aspirate culture within 2 weeks prior to admission, wound swab / fluid aspirate culture on admission, Na (sodium), ALT (alanine transaminase), mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture within 2 weeks prior to admission, faeces culture on admission, Hb (haemoglobin), sputum culture on admission, mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture on admission, faeces culture within 2 weeks prior to admission, operative severity score at 12 hours, PLT (platelets), admissions in last 30 days, blood culture, drugs taken, AMY (amylase).

Again, as in Model 1 the culture variables were removed from the analysis in backwards selection which is likely to do with the fact that they are defining the presence of infection and in this case the c-reactive protein (CRP) is a better predictor of this. Also, the outpatient attendances again are a reflection of co-morbidity, which is in itself (in the Charlson co-morbidity score) a better predictor of AKI within the model. Contrast radiology scans may have fallen out as a predictor as it may be too early in the disease process of contrast induced nephropathy to detect an acute kidney injury secondary to contrast, as this may be expected 48 - 72 hours after the insult. It is again also possible that the operative severity score fell out of the model as the detection of AKI was too early in the disease process of AKI developing after an operative procedure, and also due to the fact that other variables such as CRP again may be better predictors of the acutely unwell patient with risk of developing AKI.

The final regression model is reported in Table 21.

Table 21: Risk Model 2: Results of the multivariable ordinal logistic regression analysis to examine variables associated with new acute kidney injury (AKI) at 72 hours

Variable	Category / term	Odds Ratio (95% CI)	P-value

Age (*)	Linear term	1.78 (1.22, 2.60)	<0.001
	Quadratic term	0.97 (0.95, 1.00)	
Admission in last 2-12 months	0	1	<0.001
	1 - 2	1.41 (1.14, 1.75)	
	3 - 5	1.58 (1.20, 2.09)	
	6+	2.24 (1.57, 3.19)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.53 (0.90, 2.61)	
	Blood diseases	0.58 (0.25, 1.36)	
	Circulatory system	0.77 (0.50, 1.20)	
	Digestive system	0.84 (0.55, 1.30)	
	Genitourinary system	1.52 (0.95, 2.43)	
	Musculoskeletal	0.79 (0.39, 1.58)	
	Nervous system	0.57 (0.23, 1.38)	
	Respiratory system	0.59 (0.38, 0.91)	
	Skin	0.88 (0.46, 1.72)	
	Endocrine/metabolic	0.71 (0.34, 1.46)	
	Injury/Poisoning	1.04 (0.67, 1.60)	
	Mental disorders	0.18 (0.02, 1.32)	
	Symptoms/signs	0.78 (0.49, 1.26)	
	Other	1.33 (0.36, 4.85)	
CRP (C-Reactive Protein) - most recent result in last 30 days	Not measured	1	0.05
	Normal (≤10)	0.89 (0.65, 1.22)	
	Abnormal	1.15 (0.85, 1.55)	
HbA1c (glycated	Not measured	1	0.03

haemoglobin)			
	Measured	1.26 (1.03, 1.56)	
K (Potassium) - most recent result in last 30 days	Not measured	1	0.02
	Normal (3.5 - 5.3)	0.69 (0.50, 0.94)	
	Abnormal	0.86 (0.58, 1.26)	
Mg (Magnesium) - most recent result in last 30 days	Not measured	1	0.02
	Normal (0.7 - 1.0)	0.88 (0.65, 1.17)	
	Abnormal	1.69 (1.14, 2.50)	
Troponin – tested in last 12 months	0	1	<0.001
	1	1.42 (1.15, 1.77)	
	2+	2.19 (1.67, 2.87)	
WBC (White blood Cells) - most recent result in last 30 days	Not measured / Normal	1	0.03
	Abnormal	1.18 (1.00, 1.40)	
Modified Charlson Co-Morbidity Score	≤ 0	1	0.05
	1 - 10	1.14 (0.87, 1.49)	
	11+	1.35 (1.05, 1.75)	
	Not recorded	1.41 (1.02, 1.95)	
Baseline estimated glomerular filtration	Linear term	0.40 (0.28, 0.57)	<0.001

rate (eGFR) (**)	Quadratic term	1.11 (1.06, 1.16)	
Proteinuria (worst result)	Not done	1	0.001
	1	0.95 (0.73, 1.22)	
	2 or 3	1.52 (1.19, 1.95)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline estimated glomerular filtration rate (eGFR).

As evident from Table 21, a number of the variables retained in the final model were of borderline significance, for example modified Charlson co-morbidity score and C-Reactive Protein (p-values of 0.05). In total the final model retained twelve variables to predict new acute kidney injury (AKI) at 72 hours into hospital admission.

In the univariable analyses (Table 20, Figure 55) a linear term was used for the assessment of age, however in the multivariable analyses a better fit was found with the inclusion of a quadratic term. Again, these results are difficult to interpret from odds ratios alone. Figure 57 demonstrates the relationship between age and the adjusted predicted probability of AKI in the multivariable analysis (assuming 'average' values for all other variables), and is similar to the relationship described from the univariable analyses, however in the multivariable analysis over the age of 80 years, the increased risk plateaus.

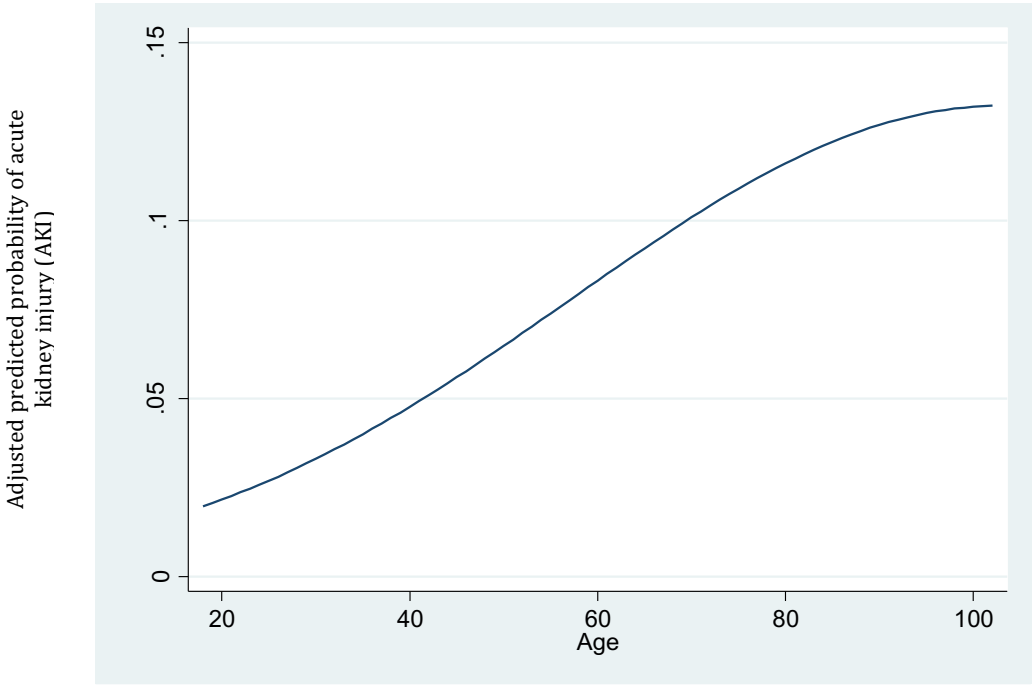


Figure 57: Risk Model 2: Relationship between age and adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis

Similar to risk Model 1 for baseline estimated glomerular filtration rate (eGFR) after adjusting for other variables in the model, there appears to be an increased probability of AKI in patients with both a lower than normal (assuming a normal eGFR of 60-120) and a higher than normal eGFR (kidney function) (Figure 58). However, in risk Model 2 the increased risk above an eGFR of 120 is less evident than in risk Model 1. Patients with lower than normal eGFR have chronic kidney disease (CKD) which is a known risk factor for AKI. A higher than normal eGFR is likely to reflect low muscle mass (eGFR is calculated from serum creatinine, which is a break down product of muscles) and potentially malnutrition, a physiological state which we would expect to pre-dispose to AKI.

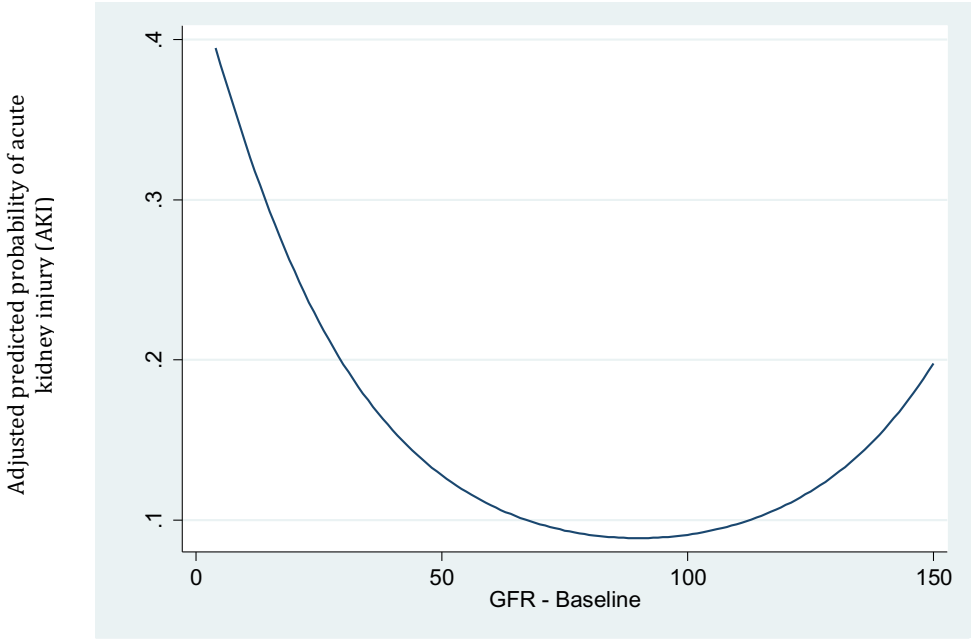


Figure 58: Risk Model 2: Relationship between estimated glomerular filtration (eGFR) and adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis

Validation

As described, 25% of the final dataset was used for validation of the developed risk model. The validation dataset consisted of 2,519 patient hospital admissions/episodes. Of those, 5 admissions were removed due to missing data leaving a final validation dataset of 2,514 admissions. Comparison between the validation and development datasets demonstrated good matching, which would be expected following random selection method.

To firstly assess validity, the patient hospital admissions/episodes were separated into risk groups based on the predicted probability of AKI. This was performed in two analyses, firstly, for the probability of any AKI as the outcome, with the risk groups as ≤10%, 10-20%, 20-40% and >40% and secondly, for the probability of either AKI stage 2 or 3 in which the risk groups were ≤2%, 2-5%, 5-10%, ≥10% (see Table 22). For each of the risk groups in the two analyses, the 'expected' risk was calculated based on predicted probabilities, and compared to the observed occurrence. The results of these analyses are reported in Table 22.

Table 22: A comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for new AKI at 72 hours

Outcome Categorisation	Risk Group	N	Mean Expected %	Observed %
Any AKI	≤ 5%	709	3.3%	4.5%
	5% - 10%	1023	7.3%	7.7%
	10% - 20%	633	13.7%	15.3%
	> 20%	149	26.9%	22.1%
AKI Stage 2 or 3	≤ 1%	1441	0.6%	0.8%
	1% - 2%	737	1.4%	2.6%
	2% - 3%	210	2.4%	3.3%
	> 3%	126	4.3%	2.4%

For the outcome 'any AKI' Table 22 demonstrates a reasonably good discrimination between risk groups, with observed results increasing with increased risk, and the categories correctly ordered. For the outcome 'AKI stage 2 or 3', the discrimination was less good. The outcome in this patient group was relatively rare, with also relatively small group sizes. In terms of observed results the outcome ('AKI stage 2 or 3') was least common in the lowest risk group (≤ 1%) as should be expected, however in the three higher risk groups (1% - 2%, 2% - 3%, > 3%), the occurrence of the outcome was similar and was highest in the second highest risk group (2% - 3%), rather than as should have been expected to be in the highest risk group (> 3%).

In terms of calibration of the model, for the outcome of 'any AKI', this was good with both a relatively good agreement between the predicted percentages and those actually observed in the data, and all observed percentages fell within the risk boundaries. However, for the prediction of the outcome 'AKI stage 2 or 3' the calibration of the model was less good with both a disparity between the predicted percentages and those actually observed in the data, and for the three

higher risk groups (1% - 2%, 2% - 3%, > 3%) the observed percentages fell outside of the risk boundaries. However, for the prediction of this outcome it could be suggested that the risk boundaries chosen were relatively tight.

Following this, based on the predicted probabilities, Receiver Operating Characteristic (ROC) curves were plotted and the Area Under the Receiver Operating Characteristic (AUROC) curves calculated, for both 'any AKI' and 'AKI stage 2 or 3' as outcomes. The ROC curve for 'any AKI' is demonstrated in Figure 59 and for 'AKI stage 2 or 3' in Figure 60. The AUROC values for both 'any AKI' and 'AKI stage 2 or 3' are reported in Table 23.

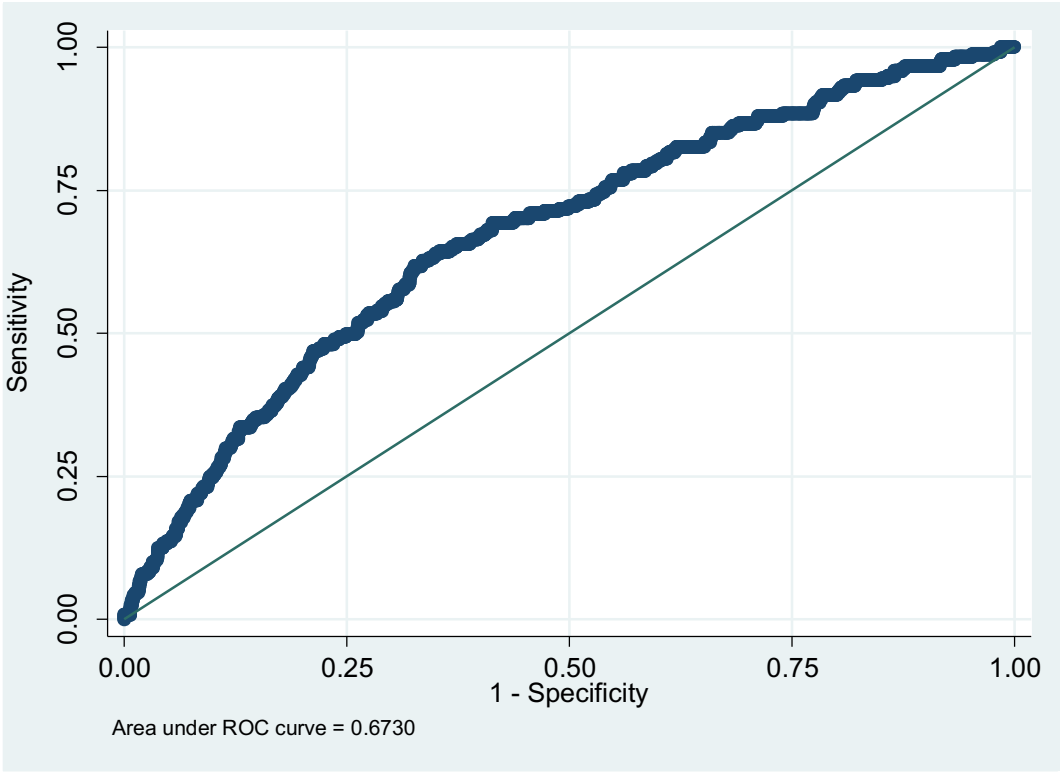


Figure 59: Risk Model 2: Receiver Operating Characteristic (ROC) curve for the prediction of 'any AKI'

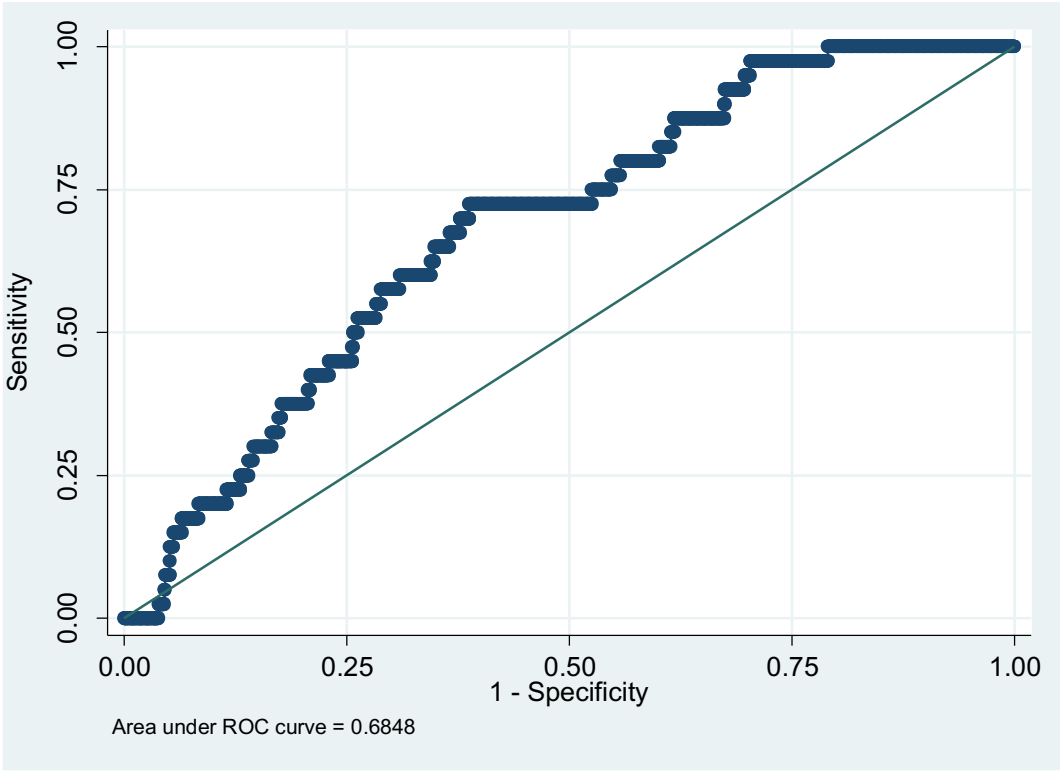


Figure 60: Risk Model 2: Receiver Operating Characteristic (ROC) Curve for the prediction of 'AKI stage 2 or 3'

Table 23: Risk Model 2: The Receiver Operating Characteristic (ROC) analyses for validation

Outcome Categorisation	**AUROC (95% CI)**	**Interpretation**
Any AKI	0.67 (0.64, 0.71)	Poor
AKI stage 2 or 3	0.68 (0.61, 0.76)	Poor

An AUROC of 0.67 (for the outcome 'any AKI') and 0.68 (for the outcome 'AKI stage 2 or 3') would suggest poor discriminatory power of risk Model 2 (predicting new AKI at 72 hours into hospital admission) being validated here. However, with both outcomes the lower confidence intervals are well above 0.5 and so could not be interpreted as a determination by chance and do suggest predictive ability, however not as great as that observed in risk Model 1.

Both in terms of development and validation, the datasets are smaller in risk Model 2 than in risk Model 1 and likely account for some of the lower predictive

ability in risk Model 2. The results from the epidemiological study in Chapter 1 demonstrate that 73.6% of patients with AKI managed in hospital, had AKI on admission, as the presence of AKI in these cases is likely a reflection of the underlying disease process (for example sepsis) that precipitated admission to hospital. The patients in risk Model 2 that develop AKI in the first 72 hours of admission may represent patient who have a rapid onset of their disease process (for example a sudden onset of acute coronary syndrome) and as is known the creatinine can take 48 hours to rise following an acute insult, to then define AKI. The fact that new AKI in the first 72 hours of admission is more difficult to predict may also suggest we are missing a key variable for prediction. One variable/s that we have not been able to ascertain from this retrospective database study are variables to define the care received during admission and in particular the quality and appropriateness of this care, as this may possibly be a determinant of which patients develop AKI while in hospital.

Finally, a Hosmer-Lemeshow test was performed to compare the numbers of patients/ admissions experiencing AKI predicted by the model, and those observed in the data, for each risk group in turn. The results of this analysis are reported in Table 24.

Table 24: Risk Model 2: A comparison of the observed numbers of AKI in each AKI group and the numbers predicted by the model using the Hosmer-Lemeshow test for validation

Outcome Categorisation	**Risk Group**	**No AKI (†) Observed N (Expected N)**	**AKI (†) Observed N (Expected N)**	**$\chi 2$ statistic (*)**	**P-value**
Any AKI	≤ 5%	677 (685)	32 (24)	6.4	0.04
	5% - 10%	944 (949)	79 (74)		
	10% - 20%	536 (546)	97 (87)		
	> 20%	116 (109)	33 (40)		
AKI Stage 2 or 3	≤ 1%	1430 (1432)	11 (9)	10.4	0.005
	1% - 2%	718 (727)	19 (10)		

	2% - 3% > 3%	203 (205) 123 (120)	7 (5) 3 (5)		

(*) With 2 degrees of freedom

(†) Or AKI stage 2 or 3 for second categorisation

This test suggests a lack of fit both for the prediction of the outcome 'any AKI' and also, and even more so, for 'AKI stage 2 or 3' as evidenced by a statistically significant difference between the numbers predicted by the model and those observed in the data. However, for the outcome 'any AKI' the lack of fit was only just statistically significant with a p-value of 0.04. The Hosmer-Lemeshow test is known to be sensitive to slight differences between predicted and observed frequencies.

For the outcome 'any AKI', in the three lowest risk groups the model under-predicts the number of cases of AKI, but however over-predicts in the highest risk group. For the outcome 'AKI stage 2 or 3' the observations are similar.

Validation in a second population

As described in the methods the calibration and discriminative ability of risk Model 2 (predicting new AKI at 72 hours into hospital admission) was then assessed in the Medway (patients presenting to Medway NHS Foundation Trust) population to provide validation in a second demographically different population. Following exclusions (as in the EKHUFT dataset) the Medway dataset included 1,585 patient hospital admissions. For each admission the predicted probability of AKI was determined from the risk model. In comparison of the EKHUFT and Medway datasets, there were differences as would be expected (hence choice of Medway as a second validation population) in terms of demographics. However, the occurrence of 'any AKI' in the two datasets was relatively similar, occurring in 8.9% of the EKHUFT population in comparison to 7.6% of the Medway population. The occurrence of 'AKI stage 2 or 3' was rare but similar in both datasets.

As with validation in the EKHUFT dataset, the patient hospital admissions/episodes were separated into the same risk groups based on the predicted probability of AKI, for both the outcomes 'any AKI' and 'AKI stage 2 or 3'. Again, the 'expected' risk was calculated based on predicted probabilities and compared to the observed occurrence in the data. The results are summarised in Table 25.

Table 25: Risk Model 2: A comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for new AKI at 72 hours in the second population (Medway)

Outcome Categorisation	Risk Category	N	Mean Expected %	Observed %
Any AKI	≤ 5%	760	3.0%	3.7%
	5% - 10%	563	6.8%	8.5%
	10% - 20%	214	13.4%	15.0%
	> 20%	48	26.5%	25.0%
AKI Stage 2 or 3	≤ 1%	1218	0.5%	0.7%
	1% - 2%	262	1.4%	0.8%
	2% - 3%	69	2.4%	1.4%
	> 3%	36	4.3%	0.0%

For the outcome 'any AKI' Table 25 demonstrates a reasonably good discrimination between risk groups, with observed results increasing with increased risk, and the categories correctly ordered. For the outcome 'AKI stage 2 or 3', the discrimination was less good, with the outcome being least common in the highest risk group (>3%). The first three risk groups were however correctly ordered, although little demonstrable difference between the lowest two risk groups (≤ 1% and 1% - 2%). The outcome in this patient group was relatively rare, with also relatively small group sizes.

In terms of calibration of the model, for the outcome of 'any AKI', this was good with both a relatively good agreement between the predicted percentages and those actually observed in the data, and all observed percentages fell within the risk boundaries. However, for the prediction of the outcome 'AKI stage 2 or 3' the calibration of the model was less good with both a disparity between the predicted percentages and those actually observed in the data, and for the three higher risk groups (1% - 2%, 2% - 3%, > 3%) the observed percentages fell outside of the risk boundaries. In these risk groups the model significantly over-predicted the occurrence of AKI.

Again, discrimination by risk Model 2 was assessed in the second population of Medway by plotting ROC curves (Figures 61 ('any AKI') and 62 ('AKI stage 2 or 3')), and calculating the AUROC (Table 26) for both the outcomes of 'any AKI' and 'AKI stage 2 or 3'.

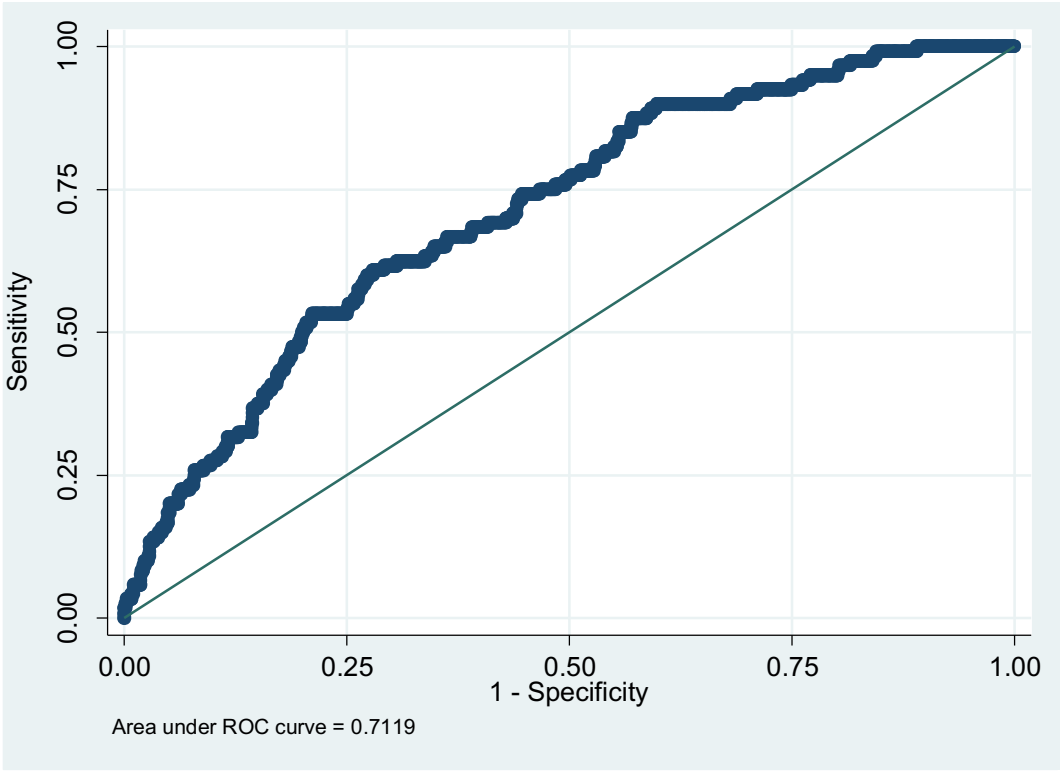


Figure 61: Risk Model 2: Receiver Operating Characteristic (ROC) curve for the prediction of 'any AKI' in the second population (Medway)

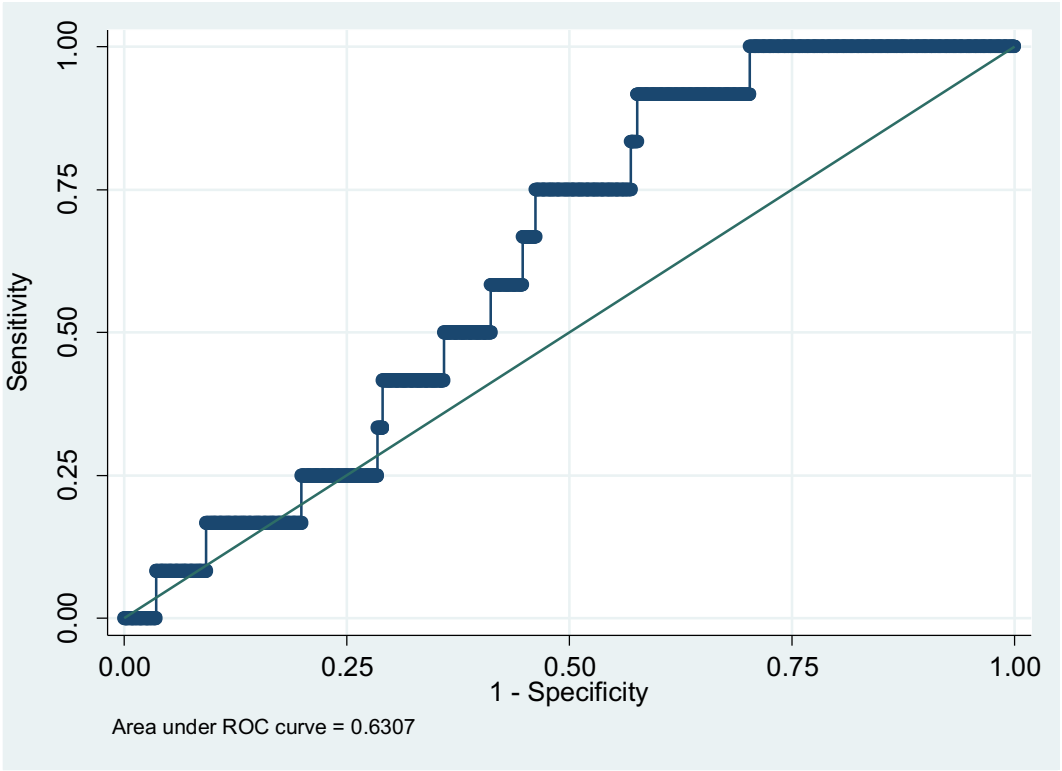


Figure 62: Risk Model 2: Receiver Operating Characteristic (ROC) Curve for the prediction of 'AKI stage 2 or 3' in the second population (Medway)

Table 26: Risk Model 2: The Receiver Operating Characteristic (ROC) analyses in the second population (Medway) for validation

Outcome Categorisation	**AUROC (95% CI)**	**Interpretation**
Any AKI	0.71 (0.67, 0.76)	Fair
AKI stage 2 or 3	0.63 (0.52, 0.75)	Poor

An AUROC of 0.71 (for the outcome 'any AKI') and 0.63 (for the outcome 'AKI stage 2 or 3') would suggest risk Model 2 (predicting new AKI at 72 hours into hospital admission) being validated here does have discriminatory power, more so for the prediction of 'any AKI' (interpreted as 'fair') and less so for the prediction of the more severe 'AKI stage 2 or 3' (interpreted as 'poor'). However, with both outcomes the lower confidence intervals are above 0.5 (only just

however for the outcome 'AKI stage 2 or 3' at 0.52) and so could not be interpreted as a determination by chance and do suggest predictive ability.

For the outcome 'any AKI' the results suggest a slightly better model performance than on the internal (EKHUFT) data, whereas for the outcome 'AKI stage 2 or 3' the performance is poorer in the second population (Medway) data than in the internal (EKHUFT) data.

Table 27: Risk Model 2: A comparison of the observed numbers of new AKI in each AKI group and the numbers predicted by the model in the second population (Medway) using the Hosmer-Lemeshow test for validation

Outcome Categorisation	**Risk Group**	**No AKI (†) Observed N (Expected N)**	**AKI (†) Observed N (Expected N)**	**$\chi 2$ statistic (*)**	**P-value**
Any AKI	≤ 5%	732 (737)	28 (23)	4.3	0.12
	5% - 10%	515 (525)	48 (38)		
	10% - 20%	182 (185)	32 (29)		
	> 20%	36 (35)	12 (13)		
AKI Stage 2 or 3	≤ 1%	1209 (1211)	9 (6.2)	4.0	0.14
	1% - 2%	260 (258)	2 (3.6)		
	2% - 3%	68 (67)	1 (1.7)		
	> 3%	36 (34)	0 (1.6)		

(*) With 2 degrees of freedom

(†) Or AKI 2 or 3 for second categorisation

The results in Table 27 suggest that for both outcomes ('any AKI' and 'AKI stage 2 or 3') the difference between the numbers predicted by the model and those observed in the data is not statistically significant, which suggests a fairly good fit of the model to the data.

Summary

The results for risk Model 2 (predicting new AKI at 72 hours into hospital admission) reported here suggest the model is better at predicting the outcome 'any AKI', than the more severe 'AKI stage 2 or 3', however the latter outcome is relatively rare in this patient population. Risk Model 2 is relatively well calibrated, however its discriminatory ability is less so than that demonstrated in risk Model 1 (predicting AKI on admission to hospital).

For the outcome of 'any AKI' when validated in the second population (Medway), risk Model 2 demonstrated both good calibration and discrimination. In terms of discrimination this was found to be even slightly better than in the primary (EKHUFT) population. For the more severe outcome of 'AKI stage 2 or 3' both the calibration and discrimination of risk Model 2 were poorer when tested in the second population (Medway).

Risk Model 3: Predicting Worsening AKI at 72 Hours

As documented in the methods section, following the defined exclusions the full dataset was split into a 'development' and a 'validation' dataset in a 3:1 ratio.

Development

The development dataset included a total of 2,333 admissions from 2,159 patients. The outcome variable of interest in this model was the presence of worsening (as described in the methods) acute kidney injury (AKI) at 72 hours into hospital admission. In order to assess which variables in the dataset were associated with the outcome variable, initially a series of univariable ordinal logistic regression analyses were performed. The results of this univariable analysis are reported in Table 28. In this analysis the odds ratios (calculated as the exponential of the parameter estimates (beta)) are reported to demonstrate the sizes of the effects, with p-values to define the significance of each variable in terms of the outcome. This univariable analysis includes both categorical variables in which the odds ratio defines the odds of worsening AKI for each category relative to a baseline category (see Table 28) and continuous variables

in which the odds ratio defines the relative change in the odds of worsening AKI for a given increase in the variable being assessed (see Table 28).

Table 28: Risk Model 3: Results of the univariable ordinal logistic regression analysis to examine variables associated with worsening acute kidney injury (AKI) at 72 hours

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	0.94 (0.86, 1.04)	0.26
Sex	Male	1	0.32
	Female	1.18 (0.86, 1.61)	
Admission in last 30 days	No	1	0.53
	Yes	0.89 (0.61, 1.129)	
Admissions in last 2-12 months	0	1	0.92
	1 - 2	0.89 (0.61, 1.29)	
	3 - 5	0.88 (0.56. 1.38)	
	6+	0.98 (0.54, 1.78)	
Outpatients attendances in last 12 months	0	1	0.42
	1 - 2	0.86 (0.57, 1.33)	
	3 - 5	0.69 (0.42. 1.11)	
	6+	1.00 (0.66, 1.52)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	6.39 (1.88, 21.7)	
	Circulatory system	1.90 (0.63, 5.69)	
	Digestive system	1.46 (0.47, 4.57)	
	Genitourinary system	2.60 (0.85, 7.94)	

	Musculoskeletal	1.67 (0.27, 10.3)	
	Nervous system	0.82 (0.08, 8.08)	
	Respiratory system	1.46 (0.48, 4.42)	
	Skin	1.15 (0.27, 4.99)	
	Endocrine/metabolic	1.06 (0.28, 4.02)	
	Injury/Poisoning	2.70 (0.84, 8.66)	
	Symptoms/signs	0.92 (0.26, 3.29)	
	Other	0.43 (0.04, 4.12)	
ALT (alanine transaminase)	Not measured	1	0.07
	Normal (≤50)	1.05 (0.69, 1.63)	
	Abnormal	1.73 (0.98, 3.05)	
AMY (amylase)	Not measured	1	0.24
	Measured	1.25 (0.86, 1.82)	
BNP (Brain Natriuretic Peptide) - 12-month average	Not measured	1	0.86
	Measured	1.09 (0.45, 2.62)	
Ca (calcium)	Not measured	1	0.92
	Normal (2.2 - 2.6)	0.93 (0.66, 1.32)	
	Abnormal	1.01 (0.47, 2.19)	
CRP (C-Reactive Protein)	Not measured	1	0.05
	Normal (≤10)	0.80 (0.32, 1.96)	
	Abnormal	1.40 (0.62, 3.17)	
Hb (Haemoglobin)	Not measured	1	0.73
	Normal (f: 11 - 15) (†)	1.02 (0.38, 2.70)	
	Abnormal	0.89 (0.34, 2.37)	

HbA1c – glycated haemoglobin - 12-month average	Not measured	1	0.85
	Normal (≤ 7.5)	1.06 (0.72, 1.58)	
	Abnormal	1.14 (0.71, 1.83)	
K (potassium)	Not measured	1	0.76
	Normal (3.5 - 5.3)	0.89 (0.43, 1.86)	
	Abnormal	1.03 (0.47, 2.27)	
Mg (magnesium)	Not measured	1	<0.001
	Normal (0.7 - 1.0)	1.29 (0.80, 2.11)	
	Abnormal	2.92 (1.71, 4.98)	
Na (sodium)	Not measured / Normal (136 – 145)	1	0.55
	Abnormal	1.10 (0.80, 1.52)	
PLT (platelets)	Not measured / Normal (150 – 400)	1	0.05
	Abnormal	1.43 (1.00, 2.05)	
Troponin	0	1	0.66
	1	0.90 (0.58, 1.39)	
	2+	1.16 (0.75, 1.78)	
WBC (White Blood Cells)	Not measured / Normal (1 – 11)	1	0.02
	Abnormal	1.51 (1.08, 2.11)	
CK (creatine kinase)	Not measured	1	0.008
	Normal (≤ 1000)	1.49 (0.73, 3.04)	
	Abnormal	4.90 (1.73, 13.9)	

Blood culture – on admission	Not taken	1	0.04
	Taken	1.47 (1.03, 2.12)	
Modified Charlson Co-Morbidity Score	≤ 0	1	0.44
	1 - 10	1.40 (0.82, 2.39)	
	11+	1.10 (0.68, 1.78)	
	Not recorded	1.45 (0.76, 2.79)	
Number of contrast radiology scans	0	1	0.05
	1+	1.77 (1.01, 3.09)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	1.18 (1.040, 1.32)	0.007
Drugs taken (+)	0	1	0.23
	1	1.09 (0.69, 1.72)	
	2 or 3	1.53 (0.90, 2.61)	
	Not recorded	1.41 (0.96, 2.07)	
Faeces Culture – within 2 weeks prior to admission	Not taken	1	0.69
	Taken	1.24 (0.42, 3.66)	
Faeces Culture – on admission	Not taken	1	0.22
	Taken	1.57 (0.78, 3.20)	

Mid-stream urine (MSU) or Catheter specimen urine (CSU) culture – within 2 weeks prior to admission	Not taken	1	0.50
	Taken	1.20 (0.71, 2.04)	
Mid-stream urine (MSU) or Catheter specimen urine (CSU) culture – on admission	Not taken	1	0.20
	Taken	1.28 (0.88, 1.85)	
Operative Severity Score at 12 hours	0	1	<0.001
	Score 1-2	1.55 (0.68, 3.52)	
	Score 3-4	4.65 (2.24, 9.67)	
Proteinuria (worst result)	Not done	1	0.84
	1	1.00 (0.65, 1.55)	
	2 or 3	1.12 (0.76, 1.65)	
Sputum culture – within 2 weeks prior to admission	Not taken	1	0.68
	Taken	0.65 (0.08, 5.17)	
Sputum culture- on admission	Not taken	1	0.02
	Taken	2.95 (1.17, 7.42)	
Wound Swab / Fluid	Not taken	1	0.10

Aspirate culture - within 2 weeks prior to admission	Taken	1.95 (0.87, 4.34)	
Wound Swab / Fluid Aspirate culture - on admission	Not taken	1	<0.001
	Taken	3.16 (1.94, 5.13)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline estimated glomerular filtration rate (eGFR)

(†) Normal range 13-18 for males

(+) Number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

The next step in risk modelling was to perform a multivariable analysis. The first step in this multivariable analysis was to assess for collinearity, and in this analysis there was no strong evidence of collinearity between predictors, and hence all predictors could be considered as independent variables in the multivariable analysis.

To determine the final model, a backwards selection method was employed which retained only the statistically significant variables (in relation to the outcome variable of worsening AKI at 72 hours). This resulted in the removal, in the following order of the variables: admissions in last 2 -12 months, faeces culture – on admission, troponin, number of contrast radiology scans, K (potassium), HbA1c, gender, AMY (amylase), BNP (Brain Natriuretic Peptide), mid-stream specimen urine (MSU) or catheter specimen urine (CSU) culture within 2 weeks prior to admission, wound swab / fluid aspirate culture within 2 weeks prior to admission, Na (sodium), admission in last 30 days, Ca (calcium), outpatient attendances in last 12 months, sputum culture within 2 weeks prior to admission, WBC (White Blood Cell count), faeces culture on admission, mid-stream specimen urine (MSU) or catheter specimen urine (CSU) culture on admission, blood culture, sputum culture on admission, modified Charlson co-

morbidity score, drugs taken, age, proteinuria, CRP (C-Reactive Protein), and ALT (alanine transaminase).

The final model is summarised in Table 29.

In this case the majority of variables are removed from the final model, and as will be demonstrated below, the model has poor performance in terms of calibration and discrimination, which suggests we do not have the correct predictors. As with the previous model it may be that one predictor of worsening AKI in hospital is the quality of care or management path of the patient with AKI which is not assessed or recorded in this database study. In this model, the operative severity score remains in the final model, which likely represents patients who have an acute admission with a surgical problem, have AKI on admission, but require an emergency operation which further worsens the AKI. In this model, unlike previous models, the c-reactive protein (CRP) which is a good marker of infection / inflammation, and a good marker that the patient is systemically unwell, is removed from the model. However, the CRP often has a lag phase in that it rises after the peak of a patient being systemically unwell, and falls after the patient has entered the recovery phase of an illness. Therefore maybe the wrong variable was chose here, instead of an absolute CRP maybe a continued rise in CRP may have provided more accurate prediction.

Table 29: Risk Model 3: Results of the multivariable ordinal logistic regression analysis to examine variables associated with worsening acute kidney injury (AKI) at 72 hours

Variable	Category / term	Odds Ratio (95% CI)	P-value
Primary diagnosis	Neoplasms	1	0.01
	Infectious diseases	7.91 (2.06, 30.3)	
	Circulatory system	2.20 (0.67, 7.23)	
	Digestive system	1.30 (0.38, 4.44)	
	Genitourinary system	3.54 (1.04, 12.0)	
	Musculoskeletal	1.48 (0.20, 10.8)	
	Nervous system	0.81 (0.07, 9.45)	

	Respiratory system	1.92 (0.58, 6.38)	
	Skin	1.27 (0.27, 6.12)	
	Endocrine/metabolic	1.03 (0.25, 4.32)	
	Injury/Poisoning	2.64 (0.74, 9.43)	
	Symptoms/signs	1.18 (0.31, 4.55)	
	Other	0.41 (0.04, 4.37)	
Mg (magnesium)	Not measured	1	0.03
	Normal (0.7 - 1.0)	1.10 (0.64, 1.90)	
	Abnormal	2.25 (1.23, 4.13)	
PLT (platelets)	Not measured / Normal (150 – 400)	1	0.06
	Abnormal	1.48 (0.99, 2.12)	
CK (creatine kinase)	Not measured	1	0.01
	Normal (≤ 1000)	1.54 (0.70, 3.39)	
	Abnormal	5.44 (1.72, 17.2)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	1.19 (1.04, 1.37)	0.01
Operative Severity Score at 12 hours	0	1	0.003
	Score 1-2	1.16 (0.44, 3.03)	
	Score 3-4	4.68 (1.91, 11.5)	
Wound Swab / Fluid Aspirate Culture - on admission	Not taken	1	0.001
	Taken	2.63 (1.49, 4.64)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline estimated glomerular filtration rate (eGFR)

As evident from Table 29 the final model consisted of 7 variables / predictors. One variable, PLT (platelets) was of borderline statistical significance (p-value 0.06), but the decision was made to retain this in the final model.

Validation

As described, 25% of the final dataset was used for validation of the developed risk model. The validation dataset consisted of 778 patient hospital admissions/episodes. Of those, 3 admissions were removed due to missing data leaving a final validation dataset of 775 admissions. Comparison between the validation and development datasets demonstrated good matching, which would be expected following random selection method.

To firstly assess validity, the patient hospital admissions/episodes were separated into risk groups based on the predicted probability of worsening AKI. Due to the smaller sample size and low occurrence of the outcome of worsening AKI in this analysis, three risk groups were used (as opposed to four in risk Models 1 and 2). These groups were: ≤ 4%, 4% - 10%, and > 10%, (see Table 30). For each of the risk groups the 'expected' risk was calculated based on predicted probabilities, and compared to the observed occurrence. The results of this analysis are reported in Table 30.

Table 30: Risk Model 3: A comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for worsening AKI at 72 hours

Risk Group	N	Mean Expected %	Observed %
≤ 4%	445	2.6%	7.4%
4% - 10%	244	5.9%	7.0%
> 10%	86	19.7%	11.6%

The results of this analysis (Table 30) suggest that the model developed here (risk Model 3) for the prediction of worsening acute kidney injury (AKI) at 72 hours into hospital admission, has poor discrimination between risk groups. The calibration of the model was also not particularly good.

Following this, based on the predicted probabilities, a Receiver Operating Characteristic (ROC) curve was plotted and the Area Under the Receiver Operating Characteristic (AUROC) curve calculated for the outcome of worsening AKI at 72 hours. The ROC curve is demonstrated in Figure 63. The AUROC was found to be 0.53 (95% CI: 0.45 to 0.61). This suggests the model has little or no discriminatory ability.

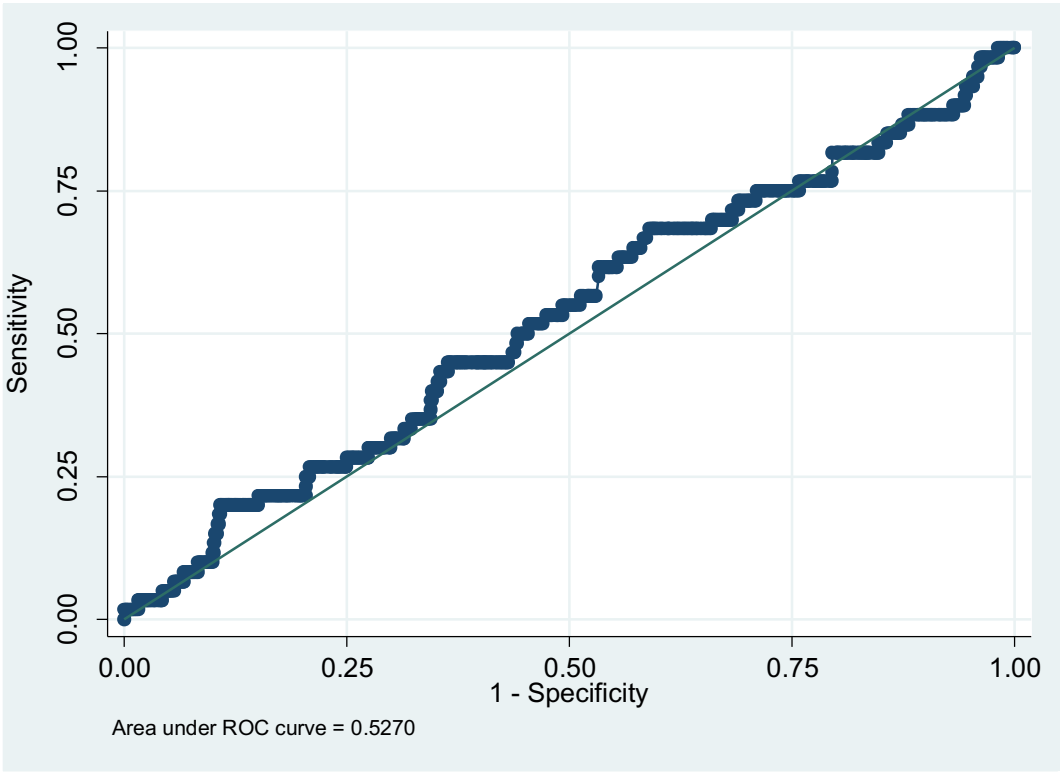


Figure 63: Risk Model 3: Receiver Operating Characteristic (ROC) Curve for the prediction of worsening acute kidney injury (AKI) at 72 hours

Finally, a Hosmer-Lemeshow test was performed to compare the numbers of patients/ admissions experiencing worsening AKI predicted by the model, and those observed in the data, for each risk group in turn. The results of this analysis are reported in the Table 31.

Table 31: Risk Model 3: A comparison of the observed numbers of worsening acute kidney injury (AKI) in each AKI group and the numbers predicted by the model using the Hosmer-Lemeshow test for validation

Risk Group	No Worsening Observed N (Expected N)	Worsening Observed N (Expected N)	$\chi 2$ statistic (*)	P-value
≤ 4%	412 (433)	33 (40)	44.8	<0.001
4% - 10%	227 (229)	17 (15)		
> 10%	76 (69)	10 (17)		

(*) With 1 degree of freedom

The results of this test (Table 31) suggest the difference between the numbers expected by the model and those observed in the data is highly significant, which suggests a lack of fit of the model to the data.

Summary

The results for risk Model 3 (predicting worsening AKI at 72 hours into hospital admission) reported here suggest that the model has a poor performance both in terms of calibration and discrimination. The poor performance of the model may be due to the fact that there are considerably fewer number in this group or that key variables have not been included in the model (e.g. physiological variables) or finally that development of AKI in this setting is subject to a random effect.

Re-analysis using NHS England standardised definition of AKI

At the end of study reported here, NHS England issued a patient safety alert on the 9th June 2014 requiring all hospital trusts to embed a national algorithm with standardised definition of AKI, in routine pathology reporting (see Appendix 9). This alert both requires trusts to alert to AKI and also ensures standardisation, which is a step towards the standardisation of care in AKI across the country, and also allows the collection of national epidemiological data in AKI. Future

studies from around the country will also be more easily comparable. In order to ensure compliance, transferability and generalisability of the work performed here across the NHS, the risk analysis of risk Models 1 (predicting AKI on admission to hospital) and 2 (predicting new AKI in 72 hours of admission), were repeated using the NHS England definition of acute kidney injury. These are reported below.

Risk Model 1: The Point of Admission to Hospital – Re-analysis using NHS England standardised definition of AKI

As documented in the methods section, following the defined exclusions the full dataset was split into a 'development' and a 'validation' dataset in a 3:1 ratio. The dataset used in this analysis employed a definition of AKI as proposed by NHS England for standardisation.

Development

The development dataset included a total of 32,626 admissions from 23,659 patients. The outcome variable of interest in this model was the presence of acute kidney injury (AKI) on admission to hospital. In order to assess which variables in the dataset were associated with the outcome variable, initially a series of univariable ordinal logistic regression analyses were performed. The results of this univariable analysis are reported in Table 32. In this analysis the odds ratios (calculated as the exponential of the parameter estimates (beta)) are reported to demonstrate the sizes of the effects, with p-values to define the significance of each variable in terms of the outcome. This univariable analysis includes both categorical variables in which the odds ratio defines the odds of being in the next highest outcome category (for example 'AKI stage 1' compared to 'no AKI'), for each category relative to a baseline category (see Table 32) and continuous variables in which the odds ratio defines the relative change in the odds of being in the next highest outcome category for a given increase in the variable being assessed (see Table 32).

Table 32: Risk Model 1: Results of the univariable ordinal logistic regression analysis to examine variables associated with acute kidney injury (AKI) on admission – re-analysis using NHS England standardised definition of AKI

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	1.21 (1.18, 1.24)	<0.001
Sex	Male	1	0.007
	Female	0.88 (0.81, 0.97)	
Admission in last 30 days	No	1	0.33
	Yes	1.05 (0.95, 1.17)	
Admissions in last 2 -12 months	0	1	0.03
	1 - 2	1.12 (1.01, 1.24)	
	3 - 5	1.19 (1.04. 1.36)	
	6+	1.08 (0.89, 1.30)	
Outpatient attendances in last 12 months	0	1	0.16
	1 - 2	0.97 (0.86, 1.09)	
	3 - 5	0.86 (0.76. 0.98)	
	6+	0.97 (0.86, 1.09)	
Admission source	Home	1	<0.001
	Not home	1.84 (1.40, 2.43)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.88 (1.37, 2.56)	
	Blood diseases	0.72 (0.44. 1.17)	
	Circulatory system	0.54 (0.41, 0.69)	

	Digestive system	0.75 (0.59, 0.97)	
	Diseases of the head/neck	0.19 (0.06, 0.60)	
	Genitourinary system	1.89 (1.48, 2.43)	
	Musculoskeletal	0.16 (0.11, 0.24)	
	Nervous system	0.27 (0.17, 0.43)	
	Respiratory system	0.88 (0.68, 1.19)	
	Skin	0.63 (0.44, 0.90)	
	Endocrine/metabolic	1.56 (1.16, 2.10)	
	Injury/Poisoning	0.31 (0.23, 0.41)	
	Mental disorders	0.49 (0.30, 0.79)	
	Symptoms/signs	0.29 (0.23, 0.37)	
	Other	0.09 (0.01, 0.64)	
Calcium (Ca) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (2.2 - 2.6)	1.06 (0.92, 1.17)	
	Abnormal	2.60 (1.99, 3.40)	
CRP (C-Reactive Protein) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (≤10)	0.71 (0.61, 0.83)	
	Abnormal	1.40 (1.25, 1.57)	
Hb (haemoglobin) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (f: 11 - 15) (†)	0.85 (0.76, 0.95)	
	Abnormal	1.42 (1.27, 1.59)	

HbA1c (glycated haemoglobin) – 12-month average	Not measured	1	<0.001
	Normal (≤ 7.5)	1.26 (1.08, 1.46)	
	Abnormal	1.79 (1.49, 2.16)	
K (potassium) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (3.5 - 5.3)	1.04 (0.95, 1.14)	
	Abnormal	1.79 (1.46, 2.19)	
Na (sodium) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (136 - 145)	0.93 (0.84, 1.03)	
	Abnormal	1.54 (1.37, 1.75)	
Potassium / sodium Combined – most recent result in last 30 days	Not measured	1	<0.001
	Both normal	0.90 (0.81, 1.01)	
	NA only abnormal	1.41 (1.23, 1.61)	
	K only abnormal	1.36 (1.01, 1.82)	
	Both abnormal	2.66 (2.00, 3.54)	
PLT (platelets) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (150 - 400)	1.01 (0.92, 1.11)	
	Abnormal	1.40 (1.21, 1.63)	

Troponin – tested in last 12 months	0	1	<0.001
	1	1.63 (1.38, 1.92)	
	2+	1.92 (1.36, 2.70)	
WBC (White Blood Cells) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (1 - 11)	0.97 (0.88, 1.07)	
	Abnormal	1.55 (1.34, 1.78)	
Blood culture – within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	2.16 (1.86, 2.51)	
	Significant	4.86 (3.83, 6.15)	
Modified Charlson co-morbidity score	≤ 0	1	<0.001
	1 - 10	1.34 (1.17, 1.54)	
	11+	1.96 (1.74, 2.21)	
	Not recorded	1.30 (1.10, 1.54)	
Baseline estimated glomerular filtration rate (GFR) (**)	Linear term	1.08 (0.61, 1.93)	<0.001
	Quadratic term	0.89 (0.76, 1.03)	
	Cubic term	1.01 (1.00, 1.02)	
Faeces culture -	Not taken	1	<0.001

within 2 weeks prior to admission			
	Taken	2.24 (1.66, 3.02)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture - within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	1.03 (0.71, 1.49)	
	Significant	1.95 (1.67, 2.29)	
Proteinuria (worst result)	Not done	1	<0.001
	1	1.28 (1.13, 1.44)	
	2 or 3	1.64 (1.44, 1.86)	
Sputum culture - within 2 weeks prior to admission	Not taken	1	0.99
	Taken	1.00 (0.61, 1.64)	
Wound swab / fluid aspirate culture - within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	0.59 (0.27, 1.25)	
	Significant	1.59 (1.22, 2.07)	

See Appendix 7 for definitions and derivations

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline eGFR

(†) Normal range 13-18 for males

(+) Total number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

The results reported in terms of odds ratios in Table 32 are clearly understandable for the categorical variables, however for the continuous variables the associations between these variables and the outcome variable of AKI are less clear. In this analysis a linear term was appropriate for age and hence this is interpretable, however the result for the other continuous variable, baseline estimated glomerular filtration rate (eGFR), is less interpretable. In this case the association with AKI is most effectively demonstrated graphically. The relationship between baseline estimated glomerular filtration rate (eGFR) and the probability of acute kidney injury (AKI) is shown in Figure 64. The outcome of 'any AKI' is plotted here.

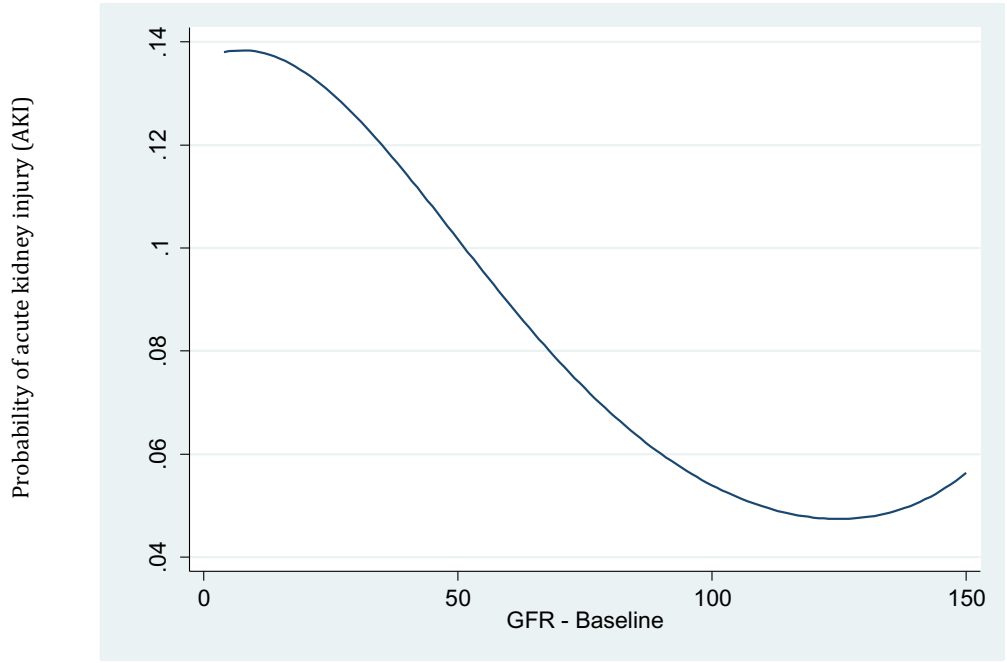


Figure 64: Risk Model 1: Relationship between baseline estimated glomerular filtration rate (eGFR) and the probability of acute kidney injury (AKI) in the univariable analysis – re-analysis using NHS England standardised definition of AKI

The probability of AKI decreases with increasing baseline estimated glomerular filtration rate (eGFR) or on the converse this can be interpreted as the poorer or

lower the kidney function, the higher the probability of AKI, which again is in concordance with the epidemiological data presented in Chapter 2, and very similar to the result described in the initial analysis using the previous definition of AKI.

The next step in risk modelling was to perform a multivariable analysis. The first step in this multivariable analysis was to assess for collinearity. An assessment for collinearity suggested this existed between haemoglobin (Hb), white blood cell count (WBC) and platelets (PLT), and also between sodium (Na) and potassium (K). As described in the initial analysis, it was apparent that these pathology blood tests were performed in the same patients. Therefore, for both of these instances of collinearity, the 'not measured' category was therefore almost equivalent where there was collinearity.

In order to deal with this collinearity, firstly in the sub-group of patients who had all three tests of Hb, WBC and PLT performed, the association between these test results and the stage of AKI was assessed. This demonstrated that only the WBC was statistically significant with respect to the outcome of AKI, as Hb and PLT were not significant when they were corrected for WBC. The decision was therefore made to only include WBC in the multivariable analysis and remove Hb and PLT. Additionally, in the subgroup of patients who had both Na and K blood tests performed, the association between these results and the stage of AKI was assessed. In this analysis it appeared that both tests were independently associated with the outcome variable of AKI. The decision was therefore made to derive a combined variable of the following categories: 'not measured' (one or both tests), 'both normal', 'Na only abnormal', 'K only abnormal' and 'both tests abnormal'.

To determine the final model, a backwards selection method was employed which retained only the statistically significant variables (in relation to the outcome variable of AKI). This resulted in the removal, in the following order of the variables: admission in last 2 – 12 months, proteinuria, sputum culture, admission in last 30 days, and wound swab/fluid aspirate culture.

As before, the removal of cultures from the final model are likely related to the fact that the c-reactive protein (CRP) is a better predictor of active infection, and the systemic effects of the infection which may precipitate an episode of AKI. Admissions in the last 30 days and also in the last 2 – 12 months may be markers of co-morbidity, which is already in the model as the co-morbidity score. Proteinuria is likely a reflection of chronic kidney disease (CKD), which is again already accounted for in the model, and hence one of the markers is removed in the backwards selection procedure.

The final regression model is reported in Table 33.

Table 33: Risk Model 1: Results of the multivariable ordinal logistic regression analysis to examine variables associated with acute kidney injury (AKI) on admission - re-analysis using NHS England standardised definition of AKI

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	1.80 (1.45, 2.24)	<0.001
	Quadratic term	0.97 (0.96, 0.99)	
Sex	Male	1	0.04
	Female	0.89 (0.80, 0.99)	
Outpatients attendances in last 12 months	0	1	<0.001
	1 - 2	0.90 (0.79, 1.02)	
	3 - 5	0.74 (0.64. 0.76)	
	6+	0.78 (0.68, 0.89)	
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.84 (1.33, 2.53)	
	Blood diseases	0.79 (0.48, 1.31)	
	Circulatory system	0.54 (0.41, 0.71)	
	Digestive system	0.86 (0.66, 1.13)	
	Diseases head/neck	0.24 (0.07, 0.79)	
	Genitourinary system	1.98 (1.52, 2.58)	
	Musculoskeletal	0.20 (0.14, 0.30)	
	Nervous system	0.35 (0.21, 0.56)	
	Respiratory system	0.80 (0.62, 1.04)	
	Skin	0.65 (0.45, 0.95)	
	Endocrine/metabolic	1.47 (1.08, 2.01)	
	Injury/Poisoning	0.36 (0.27, 0.48)	
	Mental disorders	0.56 (0.34, 0.92)	
	Symptoms/signs	0.37 (0.28, 0.48)	
	Other	0.11 (0.01, 0.76)	

Ca (Calcium) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (2.2 - 2.6)	0.86 (0.73, 1.01)	
	Abnormal	1.59 (1.16, 2.17)	
CRP (C-Reactive Protein) – most recent result in last 30 days	Not measured	1	0.02
	Normal (≤10)	0.75 (0.61, 0.92)	
	Abnormal	0.94 (0.79, 1.13)	
WBC (White Blood Cell count) – most recent result in last 30 days	Not measured	1	0.001
	Normal (1 - 11)	0.93 (0.74, 1.16)	
	Abnormal	1.28 (0.98, 1.67)	
HbA1c (glycated haemoglobin) – 12-month average	Not measured	1	0.002
	Normal (≤ 7.5)	1.12 (0.95, 1.31)	
	Abnormal	1.41 (1.16, 1.72)	
Potassium / sodium Combined – most recent results in last 30 days	Not measured	1	0.01
	Both normal	0.93 (0.79, 1.15)	
	NA only abnormal	1.09 (0.86, 1.37)	
	K only abnormal	1.04 (0.73, 1.48)	
	Both abnormal	1.64 (1.15, 2.35)	

Troponin – tested in last 12 months	0	1	<0.001
	1	1.37 (1.15, 1.65)	
	2+	1.58 (1.10, 1.65)	
Blood culture – within 2 weeks prior to admission	Not taken	1	<0.001
	Not significant	1.59 (1.34, 1.90)	
	Significant	2.81 (2.16, 3.67)	
Modified Charlson co-morbidity score	≤ 0	1	0.04
	1 - 10	1.07 (0.92, 1.25)	
	11+	1.21 (1.05, 1.39)	
	Not recorded	1.16 (0.96, 1.40)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.94 (0.51, 1.72)	<0.001
	Quadratic term	0.93 (0.80, 1.09)	
	Cubic term	1.01 (1.00, 1.03)	
Faeces culture – within 2 weeks prior to admission	Not taken	1	0.05
	Taken	1.44 (1.00, 2.09)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks prior	Not taken	1	0.01

to admission	Not significant Significant	0.79 (0.54, 1.16) 1.29 (1.07, 1.55)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline GFR

(†) Normal range 13-18 for males

(+) Total number of the following drugs taken: angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

In this multivariable analysis, as would be expected following adjustment for other variables in the model, the effect of each variable on the outcome variable of acute kidney injury (AKI) was reduced, however the effects were similar to those demonstrated in the univariable analyses.

As with the univariable analyses the continuous variables, age and baseline estimated glomerular filtration rate (eGFR), are difficult to interpret from the odds ratios. To demonstrate the relationship between these continuous variables and the outcome variable of acute kidney injury (AKI), 'average' values for the other variables in the model were assumed. Figure 65 plots age (a quadratic term was required) against the adjusted predicted probability of AKI and Figure 66 plots baseline estimated glomerular filtration rate (eGFR) against the adjusted predicted probability or AKI.

As in the univariable analysis, increasing age is associated with an increased risk of AKI, however, in the multivariable analysis this risk peaks around the age of 90. However, for baseline estimated glomerular filtration rate (eGFR) after adjusting for other variables in the model, there appears to be an increased probability of AKI in patients with both a lower than normal (assuming a normal eGFR of 60-120) and a higher than normal eGFR (kidney function) (Figure 66). In comparison with the initial analysis the re-analysis using the NHS England standardised definition of AKI demonstrates less of an increase in risk of AKI with reduction in baseline eGFR.

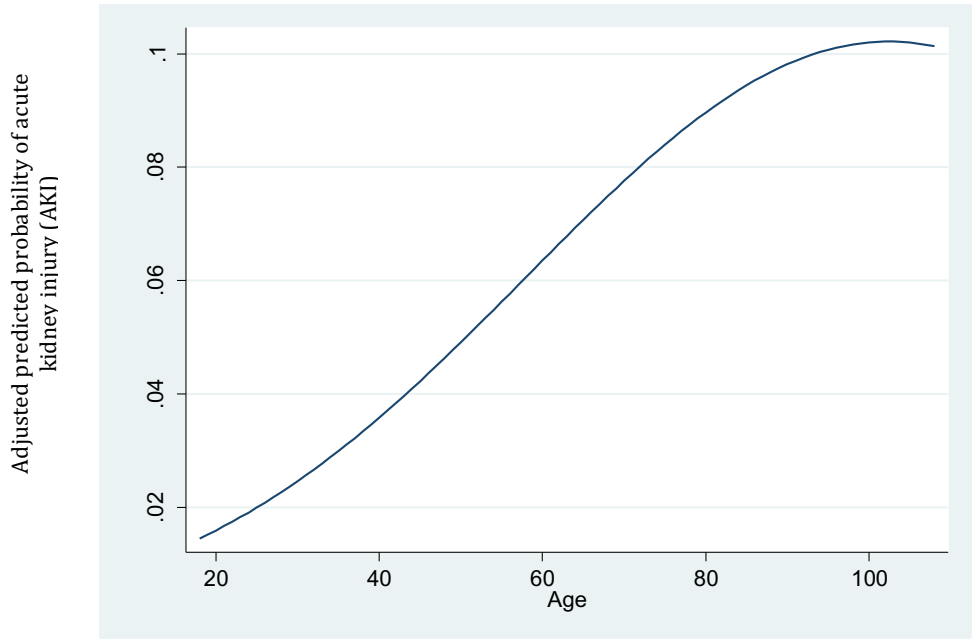


Figure 65: Risk Model 1: Relationship between age and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis - re-analysis using NHS England standardised definition of AKI

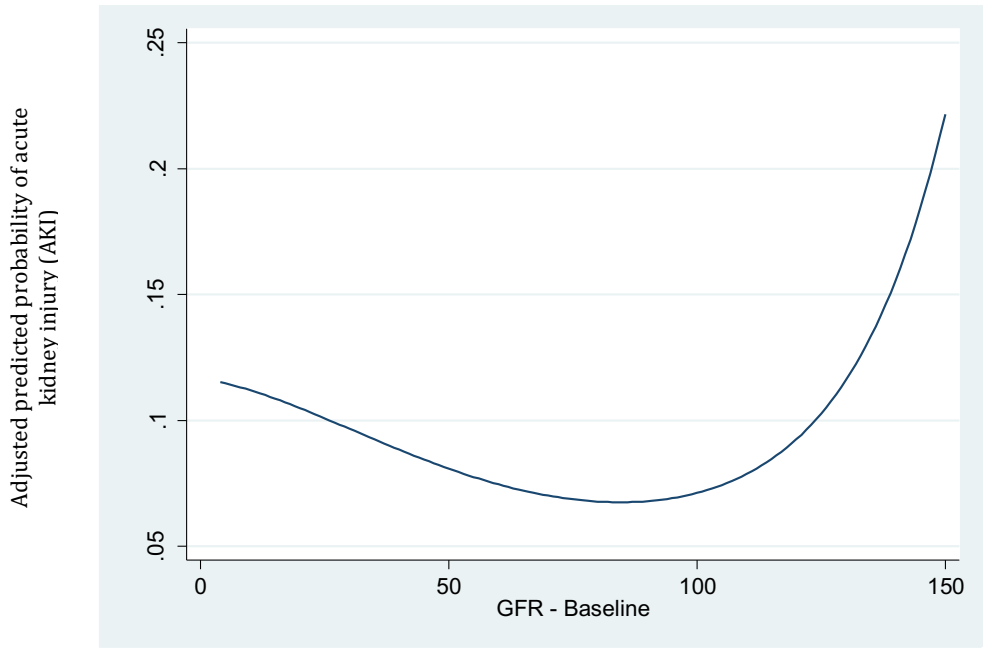


Figure 66: Risk Model 1: Relationship between estimated glomerular filtration (eGFR) and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis - re-analysis using NHS England standardised definition of AKI

Validation

As described, 25% of the final dataset was used for validation of the developed risk model. The validation dataset consisted of 10,876 patient hospital admissions/episodes. Of those, 569 admissions were removed due to missing data leaving a final validation dataset of 10,307 admissions. Comparison between the validation and development datasets demonstrated good matching, which would be expected following random selection method.

To firstly assess validity, the patient hospital admissions/episodes were separated into risk groups (slightly different risk groups were chosen compared to the initial analyses) based on the predicted probability of AKI. This was performed in two analyses, firstly, for the probability of any AKI as the outcome, with the risk groups as ≤5%, 5-10%, 10-15% and >15% and secondly, for the probability of either AKI stage 2 or 3 in which the risk groups were ≤2%, 2-5%, 5-10%, ≥10% (see Table 34). For each of the risk groups in the two analyses, the 'expected' risk was calculated based on predicted probabilities, and compared to the observed occurrence. The results of these analyses are reported in Table 34 and demonstrate a good discrimination between risk groups for both analyses (outcome of 'any AKI' and 'AKI stage 2 or 3').

Table 34: Risk Model 1: Comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for AKI on admission - re-analysis using NHS England standardised definition of AKI

Categorisation	Risk Group	N	Mean Expected %	Observed %
Any AKI	≤ 5%	4955	2.9%	2.8%
	5% - 10%	3263	7.1%	6.1%
	10% - 15%	1095	12.1%	12.4%
	> 15%	994	22.4%	20.2%
AKI stage 2 or 3	≤ 2%	5110	1.2%	0.8%
	2% - 5%	3754	3.1%	2.4%
	5% - 10%	1105	6.9%	6.9%

	> 10%	338	14.1%	11.2%

In both analyses the observed percentages fell within the boundaries of the risk groups, suggesting good calibration. Table 34 also demonstrates a good agreement between the predicted/expected percentages and those that were observed by the data, particularly for the 'any AKI' analysis.

Following this, based on the predicted probabilities, Receiver Operating Characteristic (ROC) curves were plotted and the Area Under the Receiver Operating Characteristic (AUROC) curves calculated, for both 'any AKI' and 'AKI stage 2 or 3' as outcomes. The ROC curve for 'any AKI' is demonstrated in Figure 67 and for 'AKI stage 2 or 3' in Figure 68. The AUROC values for both 'any AKI' and 'AKI stage 2 or 3' are reported in Table 35.

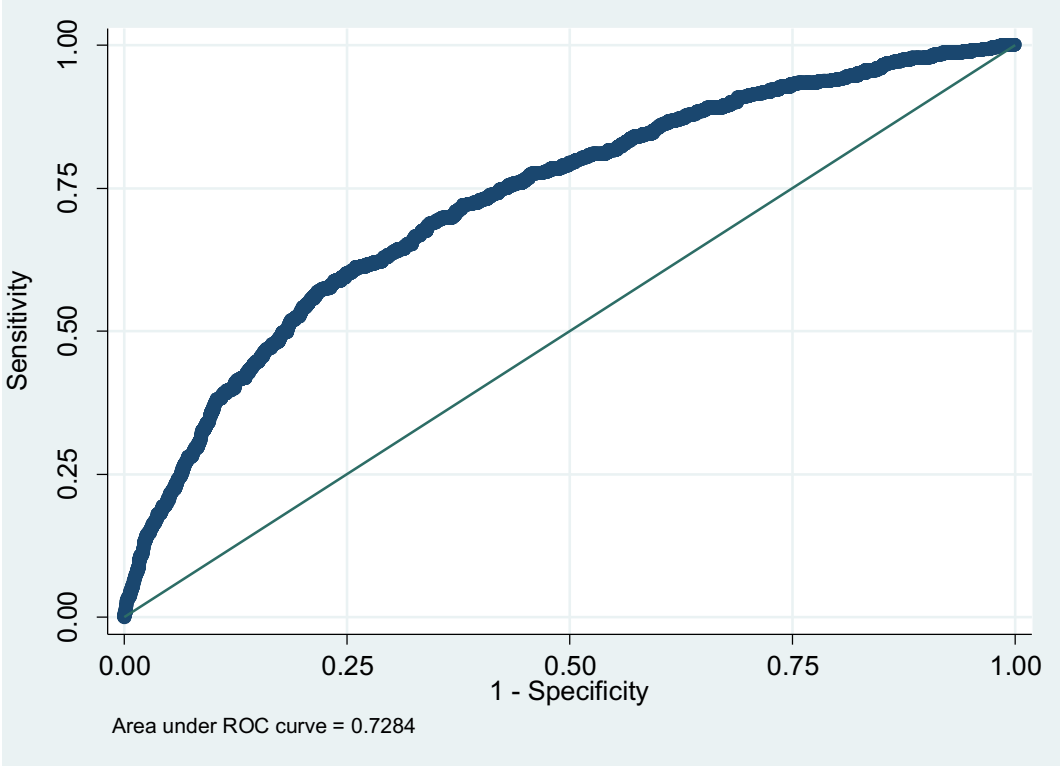


Figure 67: Risk Model 1: Receiver Operating Characteristic (ROC) curve for the prediction of 'any AKI' - re-analysis using NHS England standardised definition of AKI

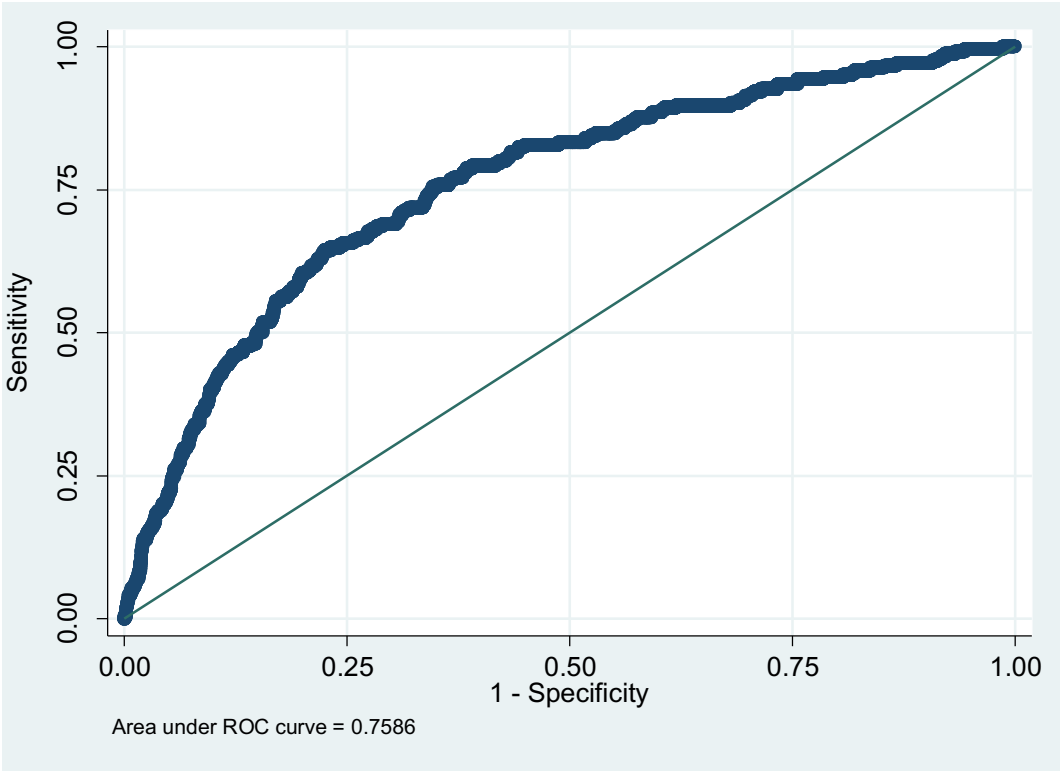


Figure 68: Risk Model 1: Receiver Operating Characteristic (ROC) Curve for the prediction of 'AKI stage 2 or 3' - re-analysis using NHS England standardised definition of AKI

Table 35: Risk Model 1: The Receiver Operating Characteristic (ROC) analyses for validation - re-analysis using NHS England standardised definition of AKI

Outcome Categorisation	**AUC (95% CI)**	**Interpretation**
Any AKI	0.73 (0.71, 0.75)	Fair
AKI Stage 2 or 3	0.76 (0.73, 0.79)	Fair

An AUROC of 0.73 for 'any AKI', and 0.76 for 'AKI stage 2 or 3' would suggest fair discriminatory power of risk Model 1 (predicting AKI on admission) being validated here. This compares well with the AUROC of 0.75 reported in the initial analysis.

Finally, a Hosmer-Lemeshow test was performed to compare the numbers of patients/ admissions experiencing AKI predicted by the model, and those

observed in the data, for each risk group in turn. The results of this analysis are reported in the Table 36.

Table 36: Risk Model 1: A comparison of the observed numbers of AKI in each AKI group and the numbers predicted by the model using the Hosmer-Lemeshow test for validation - re-analysis using NHS England standardised definition of AKI

Outcome Categorisation	**Risk Group**	**No AKI (†) Observed N (Expected N)**	**AKI (†) Observed N (Expected N)**	**$\chi 2$ statistic (*)**	**P-value**
Any AKI	≤ 5%	4815 (4809)	140 (146)	98.3	0.02
	5% - 10%	3064 (3030)	199 (233)		
	10% - 15%	959 (962)	136 (133)		
	> 15%	793 (771)	201 (223)		
AKI stage 2 or 3	≤ 2%	5069 (3916)	41 (59)	14.1	0.0009
	2% - 5%	3664 (3637)	90 (116)		
	5% - 10%	1029 (1029)	76 (76)		
	> 10%	300 (290)	38 (48)		

(*) With 2 degrees of freedom

(†) Or AKI stage 2 or 3 for second outcome categorisation

This test suggests a lack of fit both for the prediction of the outcome 'any AKI' and also, and more so, for 'AKI stage 2 or 3' as evidenced by a statistically significant difference between the numbers predicted by the model and those observed in the data. For both outcome analyses, the model slightly over-predicts the number of cases of AKI.

The Hosmer-Lemeshow test is however sensitive to slight differences between predicted and observed frequencies.

Summary

The results for risk Model 1 (predicting AKI on admission) reported here suggest that this model has fair discriminatory power and is able to separate high from low risk patients for the outcome of 'any AKI' or the more severe 'AKI stage 2 or 3'.

In terms of area under the receiver operating characteristic curve (AUROC) the model produces a value of 0.73 for the outcome of 'any AKI' and 0.76 for the outcome of 'AKI stage 2 or 3'.

These results using the NHS England standardised definition of AKI are very comparable to the initial results reported here using the lowest creatinine in the 12 months prior to admission as the baseline creatinine from which to define AKI.

Risk Model 2: Predicting New AKI at 72 Hours – Re-analysis using NHS England standardised definition of AKI

As documented in the methods section, following the defined exclusions the full dataset was split into a 'development' and a 'validation' dataset in a 3:1 ratio. The dataset used in this analysis employed a definition of AKI as proposed by NHS England for standardisation.

Development

The development dataset included a total of 11,213 admissions from 9,367 patients. The outcome variable of interest in this model was the presence of new acute kidney injury (AKI) at 72 hours into hospital admission. In order to assess which variables in the dataset were associated with the outcome variable, initially a series of univariable ordinal logistic regression analyses were performed. The results of this univariable analysis are reported in Table 37. In this analysis the odds ratios (calculated as the exponential of the parameter estimates (beta)) are reported to demonstrate the sizes of the effects, with p-values to define the significance of each variable in terms of the outcome. This

univariable analysis includes both categorical variables in which the odds ratio defines the odds of being in the next highest outcome category (for example 'AKI stage 1' compared to 'no AKI'), for each category relative to a baseline category (see Table 37) and continuous variables in which the odds ratio defines the relative change in the odds of being in the next highest outcome category for a given increase in the variable being assessed (see Table 37).

Table 37: Risk Model 2: Results of the univariable ordinal logistic regression analysis to examine variables associated with new acute kidney injury (AKI) at 72 hours - re-analysis using NHS England standardised definition of AKI

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	1.71 (1.24, 2.35)	<0.001
	Quadratic term	0.98 (0.96, 1.00)	
Sex	Male	1	0.50
	Female	0.95 (0.82, 1.10)	
Admission in last 30 days	No	1	0.66
	Yes	0.96 (0.81, 1.14)	
Admissions in last 2 - 12 months	0	1	0.47
	1 - 2	1.06 (0.89, 1.25)	
	3 - 5	1.15 (0.93. 1.42)	
	6+	0.91 (0.68, 1.23)	
Outpatients attendances in last 12 months	0	1	0.81
	1 - 2	1.02 (0.84, 1.25)	
	3 - 5	1.04 (0.84. 1.28)	
	6+	1.10 (0.90, 1.34)	

Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	1.07 (0.61, 1.86)	
	Circulatory system	1.66 (1.13, 2.45)	
	Digestive system	0.94 (0.62, 142)	
	Genitourinary system	1.70 (1.11, 2.62)	
	Musculoskeletal	0.93 (0.49, 1.78)	
	Nervous system	1.02 (0.49, 2.13)	
	Respiratory system	0.98 (0.66, 1.46)	
	Skin	1.00 (0.56, 1.77)	
	Endocrine/metabolic	0.81 (0.44, 1.47)	
	Injury/Poisoning	1.29 (0.85, 1.94)	
	Symptoms/signs	0.54 (0.34, 0.87)	
	Other	0.66 (0.33, 1.29)	
ALT (alanine transaminase) – most recent result in last 30 days	Not measured	1	0.34
	Normal (≤50)	0.89 (0.72, 1.10)	
	Abnormal	1.02 (0.76, 1.37)	
AMY (amylase) – most recent result in last 30 days	Not measured	1	0.43
	Normal (≤125)	0.89 (0.73, 1.08)	
	Abnormal	1.06 (0.65, 1.73)	
BNP (Brain Natriuretic Peptide) – 12-month average	Not measured	1	0.84
	Measured	1.05 (0.64, 1.72)	

Ca (Calcium) – most recent result in last 30 days	Not measured	1	0.15
	Normal (2.2 - 2.6)	1.04 (0.89, 1.23)	
	Abnormal	1.39 (0.99, 1.93)	
CRP (C-Reactive Protein) – most recent result in last 30 days	Not measured	1	0.002
	Normal (≤10)	0.97 (0.71, 1.32)	
	Abnormal	1.29 (0.97, 1.72)	
Hb (haemoglobin) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (f: 11 - 15) (†)	0.95 (0.57, 1.60)	
	Abnormal	1.44 (0.85, 2.43)	
HbA1c – 12-month average	Not measured	1	<0.001
	Normal (≤ 7.5)	1.36 (1.07, 1.74)	
	Abnormal	1.97 (1.46, 2.65)	
K (potassium) – most recent result in last 30 days	Not measured	1	<0.001
	Normal (3.5 - 5.3)	0.66 (0.51, 0.87)	
	Abnormal	0.93 (0.67, 1.13)	
Mg (magnesium) – most recent result in last 30 days	Not measured	1	0.08

	Normal (0.7 - 1.0)	1.18 (0.95, 1.47)	
	Abnormal	1.38 (0.97, 1.97)	
Na (sodium) – most recent result in last 30 days	Not measured / Normal (136 – 145)	1	<0.001
	Abnormal	1.35 (1.16, 1.57)	
PLT (platelets) – most recent result in last 30 days	Not measured / Normal (150 – 400)	1	0.001
	Abnormal	1.35 (1.13, 1.61)	
Troponin – tested in last 12 months	0	1	<0.001
	1	1.04 (0.86, 1.27)	
	2+	1.69 (1.36, 2.09)	
WBC (White Blood Cell count) – most recent result in last 30 days	Not measured / Normal (1 – 11)	1	<0.001
	Abnormal	1.32 (1.14, 1.54)	
CK (creatine kinase) – most recent result in last 30 days	Not measured	1	0.02
	Normal ((≤ 1000)	1.34 (0.98, 1.84)	
	Abnormal	1.79 (1.08, 2.97)	
Blood culture – on admission	Not taken	1	0.009
	Taken	1.29 (1.07, 1.56)	

Modified Charlson co-morbidity score	≤ 0	1	<0.001
	1 - 10	1.14 (0.90, 1.44)	
	11+	1.76 (1.44, 2.16)	
	Not recorded	1.24 (0.92, 1.66)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.24 (0.11, 0.48)	<0.001
	Quadratic term	1.31 (1.07, 1.59)	
	Cubic term	0.98 (0.96, 1.00)	
Faeces culture – within 2 weeks prior to admission	Not taken	1	0.90
	Taken	0.96 (0.53, 1.74)	
Faeces culture – on admission	Not taken	1	0.73
	Taken	1.10 (0.65, 1.86)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks prior to admission	Not taken	1	0.59
	Not significant	1.03 (0.60, 1.77)	
	Significant	1.17 (0.86, 1.59)	
Mid-stream specimen	Not taken	1	<0.001

of urine (MSU) or catheter specimen of urine (CSU) culture – on admission			
	Taken	1.60 (1.29, 1.97)	
Operative Severity Score at 12 hours	0	1	<0.001
	Score 1-2	1.53 (1.08, 2.17)	
	Score 3-4	2.21 (1.53, 3.20)	
Proteinuria (worst result)	Not done	1	<0.001
	1	1.32 (1.08, 1.63)	
	2 or 3	2.19 (1.80, 2.65)	
Sputum culture – within 2 weeks prior to admission	Not taken	1	0.60
	Taken	0.79 (0.33, 1.88)	
Sputum culture – on admission	Not taken	1	0.08
	Taken	1.67 (0.95, 2.93)	
Wound swab / fluid aspirate culture - within 2 weeks prior to admission	Not taken	1	0.01
	Taken	1.61 (1.11, 2.33)	
Wound swab / fluid aspirate culture - on admission	Not taken	1	<0.001
	Taken	1.81 (1.38, 2.37)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline GFR

(†) Normal range 13-18 for males

(+) Total Number of the following drugs taken: angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAID), diuretics

The results reported in terms of odds ratios in Table 37 are clearly understandable for the categorical variables, however for the continuous variables the associations between these variables and the outcome variable of AKI are less clear. These associations are most effectively demonstrated graphically. The relationship between these continuous variables (age and baseline estimated glomerular filtration rate (eGFR)) and the probability of acute kidney injury (AKI) are shown in Figures 69 (age) and 70 (eGFR) respectively. The outcome of 'any AKI' is plotted here.

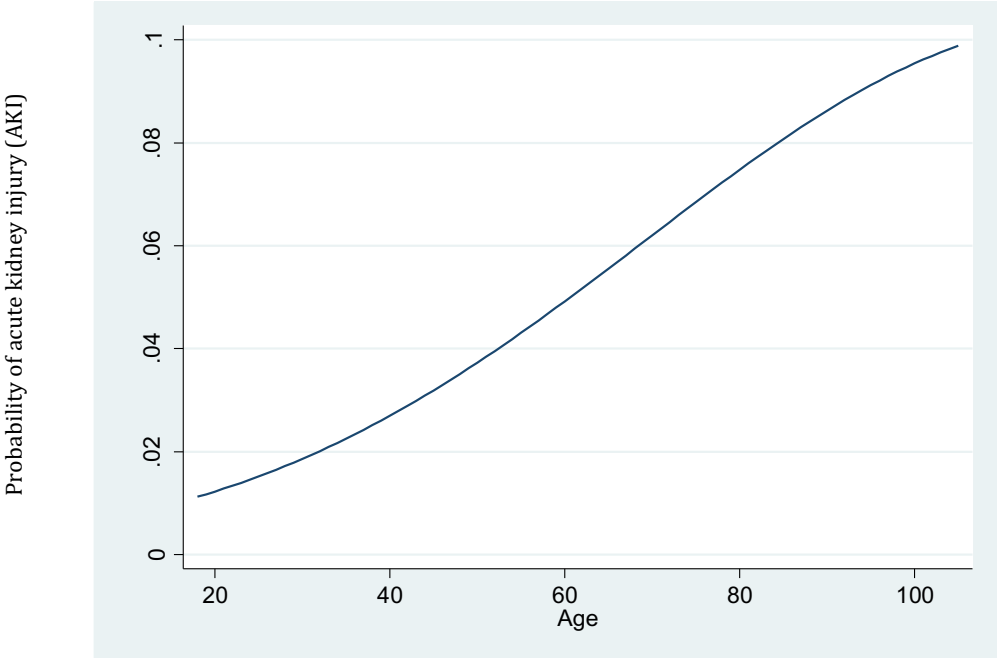


Figure 69: Risk Model 2: Relationship between age and the probability of acute kidney injury (AKI) in the univariable analysis - re-analysis using NHS England standardised definition of AKI

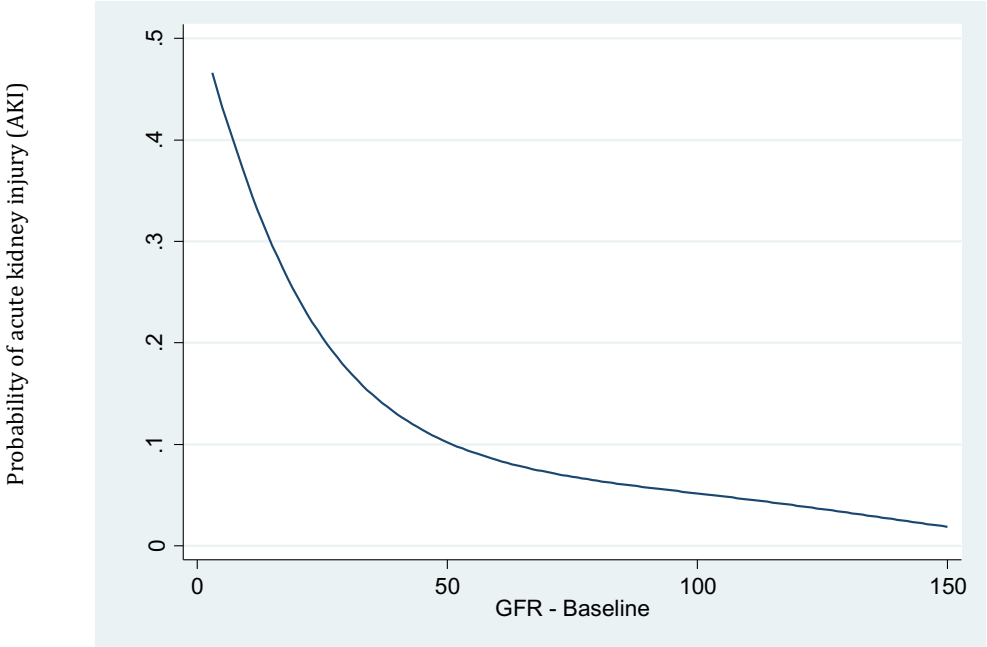


Figure 70: Risk Model 2: Relationship between baseline estimated glomerular filtration rate (eGFR) and the probability of acute kidney injury (AKI) in the univariable analysis - re-analysis using NHS England standardised definition of AKI

The next step in risk modelling was to perform a multivariable analysis. The first step in this multivariable analysis was to assess for collinearity, and in this analysis there was no strong evidence of collinearity between predictors, and hence all predictors could be considered as independent variables in the multivariable analysis.

To determine the final model, a backwards selection method was employed which retained only the statistically significant variables (in relation to the outcome variable of new AKI at 72 hours). This resulted in the removal, in the following order of the variables: faeces culture – within 2 weeks prior to admission, admissions in the last 2 – 12 months, outpatient attendances in the last 12 months, mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – within 2 weeks prior to admission, sputum culture – within 2 weeks prior to admission, admission in the last 30 days, troponin, wound swab / fluid aspirate culture – within 2 weeks prior to admission, gender, CRP (C-Reactive Protein), BNP (Brain Natriuretic Peptide), CK (creatine kinase), faeces culture – on admission, modified Charlson co-morbidity score, sputum culture –

on admission, Mg (magnesium), Ca (calcium), Hb (haemoglobin), and AMY (amylase).

As would be expected the cultures on admission have been retained in the final model. As discussed previously it can take 48 hours for the creatinine to rise in an episode of acute kidney injury and so this situation may reflect a patient presenting to hospital with an acute onset of sepsis, defined by the sending of cultures in this database study, and then the creatinine rises in the 48-72 hours post admission and defines AKI. As in all analyses the primary diagnosis is a key variable which predicts both patients with AKI on admission, or those who will develop AKI in the first 72 hours of admission. In this analysis interestingly both co-morbidity and c-reactive protein (CRP) have fallen out of the final model. In the case of CRP, the cultures, white blood cells (WBC) and platelets (PLT) for example may be providing markers of infection and hence risk of AKI over and above the utility of the CRP. The operative severity score remains in the final model which represents the risk of an operation in the development of AKI.

The final regression model is reported in Table 38.

Table 38: Risk Model 2: Results of the multivariable ordinal logistic regression analysis to examine variables associated with new acute kidney injury (AKI) at 72 hours - re-analysis using NHS England standardised definition of AKI

Variable	Category / term	Odds Ratio (95% CI)	P-value
Age (*)	Linear term	1.17 (1.08, 1.26)	<0.001
Primary diagnosis	Neoplasms	1	<0.001
	Infectious diseases	0.95 (0.54, 1.68)	
	Circulatory system	1.75 (1.17, 2.61)	
	Digestive system	1.07 (0.70, 1.64)	
	Genitourinary system	1.54 (0.99, 2.39)	
	Musculoskeletal	0.85 (0.43, 1.67)	
	Nervous system	1.21 (0.58, 2.59)	

	Respiratory system	0.96 (0.64, 1.45)	
	Skin	0.80 (0.44, 1.45)	
	Endocrine/metabolic	0.71 (0.38, 1.32)	
	Injury/Poisoning	1.16 (0.75, 1.80)	
	Symptoms/signs	0.71 (0.44, 1.16)	
	Other	0.67 (0.33, 1.35)	
ALT (alanine transaminase) – most recent result in last 30 days	Not measured	1	0.04
	Normal (≤50)	0.89 (0.71, 1.11)	
	Abnormal	1.21 (0.88, 1.67)	
HbA1c – 12-month average	Not measured	1	0.01
	Normal (≤ 7.5)	1.09 (0.84, 1.41)	
	Abnormal	1.63 (1.17, 2.26)	
K (potassium) – most recent result in last 30 days	Not measured	1	0.004
	Normal (3.5 - 5.3)	0.66 (0.50, 0.87)	
	Abnormal	0.82 (0.59, 1.15)	
Na (sodium) – most recent result in last 30 days	Not measured / Normal (136 – 145)	1	0.009
	Abnormal	1.24 (1.05, 1.45)	
PLT (platelets) – most recent result in last 30 days	Not measured / Normal (150 – 400)	1	0.001

	Abnormal	1.34 (1.12, 1.61)	
WBC (White Blood Cells) – most recent result in last 30 days	Not measured / Normal	1	<0.001
	Abnormal	1.33 (1.14, 1.56)	
Blood culture – on admission	Not taken	1	0.05
	Taken	1.24 (1.01, 1.53)	
Baseline estimated glomerular filtration rate (eGFR) (**)	Linear term	0.16 (0.07, 0.35)	<0.001
	Quadratic term	1.46 (1.17, 1.81)	
	Cubic term	0.98 (0.96, 0.99)	
Mid-stream specimen of urine (MSU) or catheter specimen of urine (CSU) culture – on admission	Not taken	1	0.02
	Taken	1.31 (1.05, 1.64)	
Operative Severity Score at 12 hours	0	1	<0.001
	Score 1-2	1.76 (1.18, 2.61)	
	Score 3-4	2.20 (1.48, 3.29)	
Proteinuria (worst result)	Not done	1	0.001
	1	1.02 (0.82, 1.28)	
	2 or 3	1.35 (1.08, 1.68)	

Wound swab / fluid aspirate culture - on admission	Not taken	1	<0.001
	Taken	1.77 (1.32, 2.38)	

(*) Odds ratio given for a 10-unit increase in age

(**) Odds ratio given for a 20-unit increase in baseline estimated glomerular filtration rate (eGFR).

As evident from Table 38, the variable 'blood culture – on admission' was of borderline significance (p-value of 0.05), however the decision was made to keep this variable in the final model. In total the final model retained fourteen variables to predict new acute kidney injury (AKI) at 72 hours into hospital admission.

In the univariable analysis for the assessment of age, both linear and quadratic terms were required, however in the multivariable analysis after adjusting for other variables in the model, the quadratic term was no longer required.
Figure 71 demonstrates the relationship between age and the adjusted predicted probability of AKI in the multivariable analysis (assuming 'average' values for all other variables), which demonstrates a steady increase in risk of AKI with increasing age, which is similar to the result in the univariable analysis.

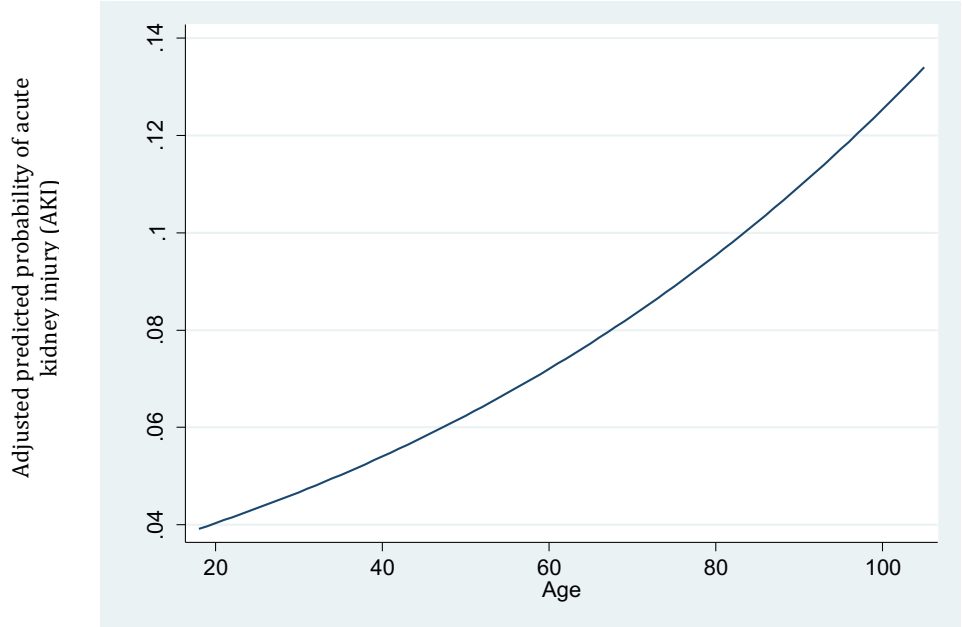


Figure 71: Risk Model 2: Relationship between age and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis - re-analysis using NHS England standardised definition of AKI

Figure 72 demonstrates the relationship between baseline estimated glomerular filtration rate (eGFR) and the adjusted predicted probability of AKI in the multivariable analysis (assuming 'average' values for all other variables), which demonstrates an increased probability of AKI in patients with a lower than normal (assuming a normal eGFR of 60-120) eGFR (kidney function) (Figure 72). This differs from the results of the initial analysis (using a definition of AKI with a baseline creatinine defined as the lowest creatinine in the 12 months prior to admission) in which there was in addition, an increased risk of AKI with an eGFR of greater than 120.

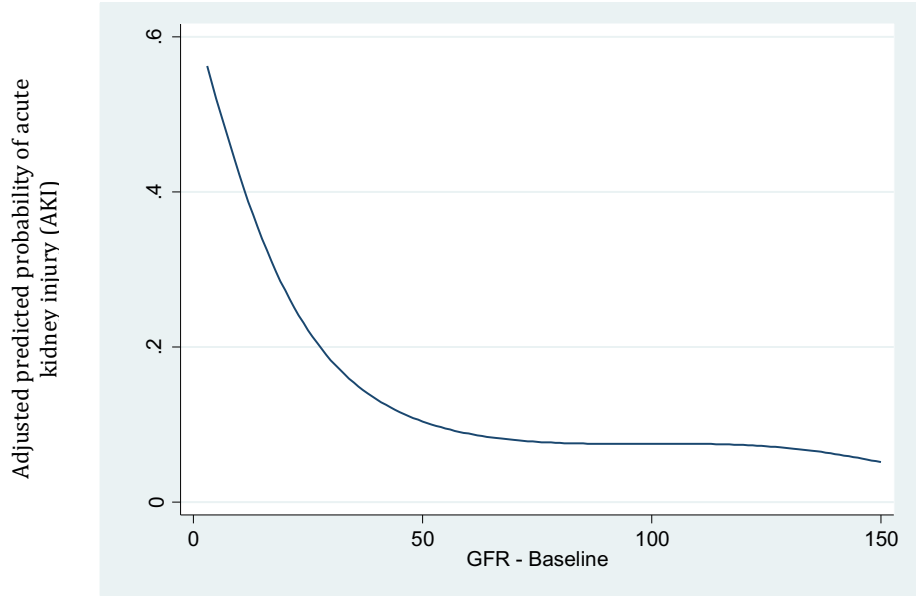


Figure 72: Risk Model 2: Relationship between estimated glomerular filtration (eGFR) and the adjusted predicted probability of acute kidney injury (AKI) in the multivariable analysis - re-analysis using NHS England standardised definition of AKI

Validation

As described, 25% of the final dataset was used for validation of the developed risk model. The validation dataset consisted of 3,738 patient hospital admissions/episodes. Of those, 200 admissions were removed due to missing

data leaving a final validation dataset of 3,538 admissions. Comparison between the validation and development datasets demonstrated good matching, which would be expected following random selection method.

To firstly assess validity, the patient hospital admissions/episodes were separated into risk groups based on the predicted probability of AKI. In this analysis in comparison to the initial analyses performed slightly different risk groups were chosen, and only the outcome 'any AKI' was analysed. The risk groups were ≤5%, 5-10%, 10-15% and >15% (see Table 39). For each of the risk groups the 'expected' risk was calculated based on predicted probabilities, and compared to the observed occurrence. The result of this analysis is reported in Table 39.

Table 39: Risk Model 2: A comparison of the expected with the observed probabilities of acute kidney injury (AKI) in the different risk groups for new AKI at 72 hours - re-analysis using NHS England standardised definition of AKI

Outcome Categorisation	Risk Group	N	Mean Expected %	Observed %
Any AKI	≤ 5% 5% - 10% 10% - 15% > 15%	1662 1271 389 216	3.3% 6.9% 12.0% 21.3%	4.2% 8.9% 12.9% 20.8%

For the outcome 'any AKI' Table 39 demonstrates a reasonably good discrimination between risk groups, with observed results increasing with increased risk, and the categories correctly ordered.

In terms of calibration of the model, for the outcome of 'any AKI', this was good with both a relatively good agreement between the predicted percentages and those actually observed in the data, and all observed percentages fell within the risk boundaries.

Following this, based on the predicted probabilities, a Receiver Operating Characteristic (ROC) curve was plotted and the Area Under the Receiver Operating Characteristic (AUROC) curve calculated for the outcome 'any AKI'. The ROC curve for 'any AKI' is demonstrated in Figure 73. The AUROC value for the outcome 'any AKI' is reported in Table 40.

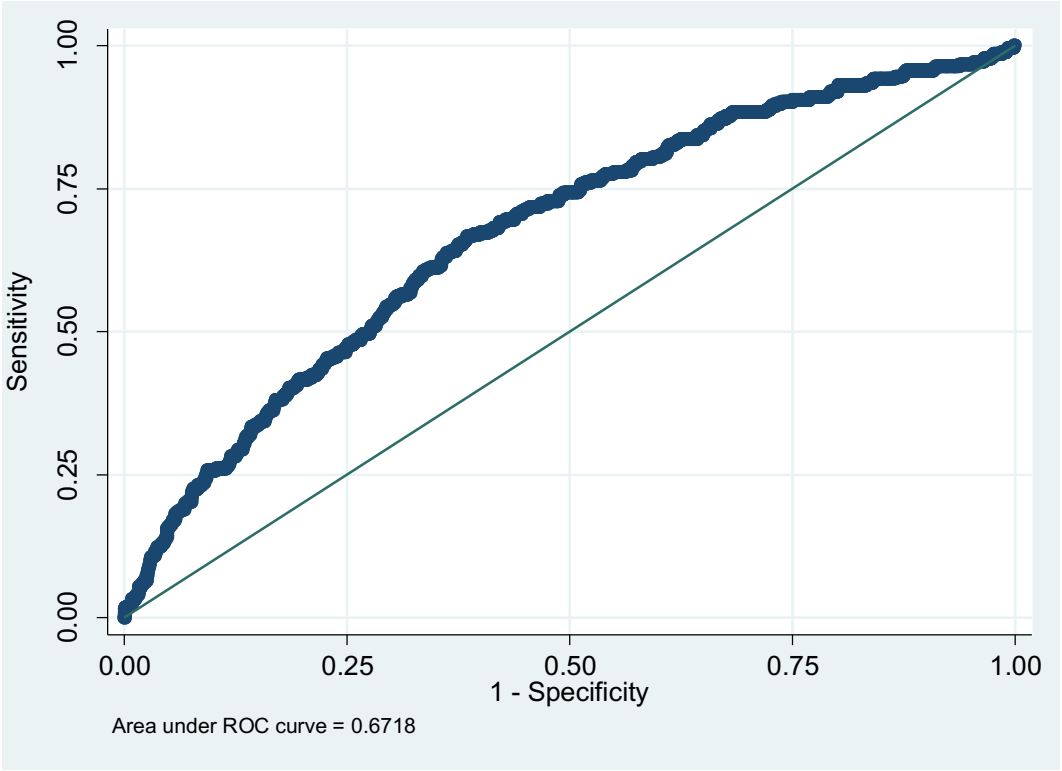


Figure 73: Risk Model 2: Receiver Operating Characteristic (ROC) curve for the prediction of 'any AKI' - re-analysis using NHS England standardised definition of AKI

Table 40: Risk Model 2: The Receiver Operating Characteristic (ROC) analyses for validation - re-analysis using NHS England standardised definition of AKI

Outcome Categorisation	**AUC (95% CI)**	**Interpretation**
Any AKI	0.67 (0.64, 0.70)	Poor

An AUROC of 0.67 would suggest poor discriminatory power of risk Model 2 (predicting new AKI at 72 hours into hospital admission) being validated here. However, the lower confidence intervals are well above 0.5 and so could not be

interpreted as a determination by chance and do suggest predictive ability, however not as great as that observed in risk Model 1. This does however compare very well with that reported in the initial analysis.

Finally, a Hosmer-Lemeshow test was performed to compare the numbers of patients/ admissions experiencing AKI predicted by the model, and those observed in the data, for each risk group in turn. The results of this analysis are reported in the Table 41.

Table 41: Risk Model 2: A comparison of the observed numbers of AKI in each AKI group and the numbers predicted by the model using the Hosmer-Lemeshow test for validation - re-analysis using NHS England standardised definition of AKI

Outcome Categorisation	**Risk category**	**No AKI Observed N (Expected N)**	**AKI Observed N (Expected N)**	**$\chi 2$ statistic (*)**	**P-value**
Any AKI	≤ 5% 5% - 10% 10% - 15% > 15%	1593 (1607) 1159 (1183) 339 (342) 171 (170)	69 (55) 112 (88) 50 (47) 45 (46)	10.9	0.004

(*) With 2 degrees of freedom

(†) Or AKI stage 2 or 3 for second categorisation

This test suggests a lack of fit for the prediction of the outcome 'any AKI' as evidenced by a statistically significant difference between the numbers predicted by the model and those observed in the data. The Hosmer-Lemeshow test is known to be sensitive to slight differences between predicted and observed frequencies.

For the outcome 'any AKI', in the two lowest risk groups the model under-predicts the number of cases of AKI.

Summary

The results for risk Model 2 (predicting new AKI at 72 hours into hospital admission) reported here suggest that risk Model 2 is relatively well calibrated, however its discriminatory ability is less so than that demonstrated in risk Model 1 (predicting AKI on admission to hospital), with an area under the receiver operating characteristic curve (AUROC) of 0.67 (interpreted as poor) for the outcome of 'any AKI'.

These results using the NHS England standardised definition of AKI are very comparable to the initial results reported here using the lowest creatinine in the 12 months prior to admission as the baseline creatinine from which to define AKI.

Summary of Results

Table 42 summarises the outcomes in terms of discriminatory power of the risk models developed in this study. Risk Model 1, predicting the risk of a patient already having acute kidney injury (AKI) on admission, demonstrates the best discriminatory ability with an AUROC of 0.75 to predict any AKI and 0.75 to predict AKI stage 2 or 3 in the East Kent Hospitals University NHS Foundation Trust (EKHUFT) dataset. This AUROC (between 0.7 - 0.8) is interpreted as providing a 'fair' discriminatory ability. When the risk model is validated in a second population, the Medway NHS Foundation Trust dataset, the discriminatory ability of the model falls slightly to an AUROC of 0.72 to predict any AKI and 0.71 to predict AKI stage 2 or 3, as might be expected in a demographically very different population. This does however remain a very similar outcome and interpreted as the model again having 'fair' discriminatory ability in the second population. This demonstrates good transferability and generalizability of the risk model.

When the analysis was re-run in the EKHUFT dataset, using the NHS England standardised algorithm to define AKI, the discriminatory ability of Risk Model 1 to predict the risk of a patient already having AKI on admission was very similar

to that produced in the initial analysis in which AKI was defined using the lowest creatinine in the 12 months prior to admission. The AUROC was 0.73 using the NHS England algorithm in comparison to 0.75 in the initial analysis for predicting any AKI, and 0.76 using the NHS England algorithm in comparison to 0.75 in the initial analysis for predicting AKI stage 2 or 3.

In Risk Model 2, to predict new AKI at 72 hours, in each validation dataset the model showed less discriminatory ability to predict either any AKI or AKI stage 2 or 3 than in Risk Model 1. Again the model showed similar discriminatory ability in all validation populations, however in this case the ability of the model to predict any AKI was greater in the second population (Medway), with an AUROC of 0.71 in comparison to the initial population (EKHUFT) with an AUROC of 0.67. The converse was true in predicting AKI stage 2 or 3, with the ability of the model to predict AKI stage 2 or 3 being greater in the initial population (EKHUFT) with an AUROC of 0.68, in comparison to the second population (Medway) of 0.63. In this respect we can say that the model was better at predicting AKI stage 2 or 3 in the initial population (EKHUFT), and better at predicting any AKI in the second population (Medway).

Again on re-analysis using the NHS England algorithm to define AKI, the result was very similar to the initial results using the lowest serum creatinine in the 12 months prior to admission as the baseline creatinine from which to define AKI. This further validation using the NHS England algorithm to define AKI was important as this algorithm is now used across the country to define AKI in clinical practice, as mandated by NHS England.

The development of Risk Model 3 to predict worsening AKI at 72 hours produced an AUROC of 0.53 in the EKHUFT validation dataset suggesting no discriminatory ability of the model and therefore further validation was not performed using this model.

Table 42: Summary of risk modelling results with comparison of outcomes between models and across populations

		Initial Analysis – Validation Index Population - EKHUFT Dataset		***Initial Analysis – Validation in 2nd Population – Medway Dataset***		***Re-Analysis Using NHS England Algorithm – EKHUFT Dataset***	
Risk Model	**Outcome Categorisation**	**AUROC (95% CI)**	**Interpretation**	**AUROC (95% CI)**	**Interpretation**	**AUROC (95% CI)**	**Interpretation**

1 – Point of Admission to Hospital	Any AKI	0.75 (0.74,0.77)	Fair	0.72 (0.71,0.74)	Fair	0.73 (0.71,0.75)	Fair
	AKI Stage 2 or 3	0.75 (0.73,0.78)	Fair	0.71 (0.68,0.75)	Fair	0.76 (0.73,0.79)	Fair
2 – Predicting New AKI at 72 Hours	Any AKI	0.67 (0.64,0.71)	Poor	0.71 (0.67,0.76)	Fair	0.67 (0.64,0.70)	Poor
	AKI Stage 2 or 3	0.68 (0.61,0.76)	Poor	0.63 (0.52,0.75)	Poor		
3 – Predicting Worsening AKI at 72 Hours	Worsening AKI	0.53 (0.45,0.61)	No Discrimination				

Chapter Summary

The work described in this chapter has defined a clinical practice algorithm for risk assessment within the first 24 hours of hospital admission. Traditional regression methods identified key variables which predict AKI both on admission and at 72 hours post admission. Validation demonstrated an AUROC of 0.75 and 0.68 respectively. Predicting worsening AKI during admission was unsuccessful. This study provides valuable evidence of relationships between key variables and AKI and has developed a clinical algorithm and risk models for risk assessment within the first 24 hours of admission. This work provides a firm basis and direction in the literature to guide further risk model development in this area. Future work may include continuous modelling, non-linear modelling and interaction exploration in order to further refine models.

With now validated models the next step would be to deliver a clinical alert using both the risk models and clinical alert system developed here to alert to a patient at risk of AKI, in real-time to the point of care. Ultimately then a health technology assessment is required of both AKI and AKI risk alerting in clinical care, in terms of clinical benefit and cost effectiveness.

Chapter 6: Discussions and Conclusion

Acute kidney injury (AKI), previously known as acute renal failure, is an all too common clinical problem characterised by an acute decline in renal function, the result of which ranges from minimal alteration in serum creatinine to anuric renal failure requiring renal replacement therapy (RRT). Even without the need of RRT, AKI may impact on a patient's clinical course with complications such as fluid overload, acidosis and hyperkalaemia; all of which may lead to an increase in morbidity, length of stay and ultimately mortality both long and short term. With growing literature and a now standardised definition, AKI has become an increasingly recognised public health issue with a growing impetus to improve management.

The overarching aim of this PhD thesis was to begin down a path of quality improvement measures to improve patient safety in AKI. Firstly, by defining and highlighting the real impact of AKI (Chapter 2), secondly, developing methods to improve recognition of AKI (Chapter 3), allowing early intervention in patients with AKI and finally, developing mathematical models to predict patients at risk of AKI (Chapter 5) in order to allow management decisions to provide the best form of treatment, namely prevention.

With the accepted and validated definitions of AKI reported in the literature (Chapter 1), the first stage of the work here was to assess the 'true' impact of this disease. Previous work reported in the literature (Chapter 1) had employed varying definitions and often in the setting of a large teaching hospital, not providing sufficient insight into the incidence and outcomes of AKI in a 'typical' general hospital setting. The epidemiological study reported in Chapter 2 (published form in Appendix 2) comes closer to the real incidence and outcomes of AKI managed in-hospital. In this study fifteen per cent of all admissions sustained an episode of AKI with increased subsequent short and long term morbidity and mortality, even in those with AKI stage 1. In comparison with patients with no AKI those with AKI stage 1 had a 52% longer length of stay

(LOS) in hospital, a 2.8-fold increased risk of admission to the intensive therapy unit (ITU), a 39% longer ITU stay (in those who went to ITU), and a 2.4-fold greater in-hospital mortality. Furthermore, patients with AKI stage 1 had twice the long-term risk of death, a 33% higher likelihood of an increase in care, and a 42% higher risk of re-admission within 30 days. In those patients with AKI stage 3 (the subject of the NCEPOD report) [100] hospital LOS doubled, there was a 22 times higher risk of admission to ITU and ITU LOS was also doubled, consistent with national data from the Intensive Care National Audit and Research Centre. Acute RRT support was required in 13.1% of patients with AKI stage 3. Hospital mortality was 26-fold greater and in those surviving to leave hospital there was a 5.5-fold increased risk of subsequent death. Patients with AKI stage 3 had a 7% higher risk of requiring an increase in care and had a 54% higher risk of re-admission within 30 days than patients with no AKI. Overall, 0.45% of patients with AKI and 3.40% of patients with AKI stage 3 subsequently required chronic RRT.

The increase in morbidity experienced in patients with AKI confers an increased burden and cost to the healthcare economy, which with the aid of this data, can be quantified and has now been performed in a joint study with Marion Kerr (Health Economist for the Department of Health) and published in the literature (Appendix 3).[106] This study suggests that the annual number of excess inpatient deaths with AKI in England may be greater than 40,000 and the annual cost of AKI-related inpatient care in England is estimated at £1.02 billion (Appendix 3). [106]

With a clearer definition of the clinical problem of acute kidney injury, the next step was to begin to improve its recognition and management. The NCEPOD report [100] (see Chapter 1), suggested that in 14% of patients who die from acute kidney injury (AKI), the AKI may be avoidable; and in patients developing AKI post admission, a fifth were deemed predictable and avoidable and 43% judged to have an unacceptable delay in recognising AKI. [100]

The management of AKI is not complex and involves simple assessment and interventions, such as fluid assessment and correction of hypovolaemia and hypotension, withholding nephrotoxic medications, assess drug dosages in respect to level of kidney function, looking for and treating infection early, recognising and treating hypoxia, checking for acidosis, urinalysis, renal tract ultrasound and daily testing of kidney function. The NCEPOD report [100] however suggests that these things are not done effectively.

Chapter 3 documents the development of a simple reporting/alerting tool to define all patients within a hospital trust who have acute kidney injury, the stage of their disease, demographic details, clinical team and location within the hospital, to allow focused intervention by critical care outreach nurses and specialist renal consultants. The intervention also included the placing of a sticker into the clinical notes of a patient with AKI to firstly alert to the presence of AKI to all members of the healthcare professional team, but also to provide clear both generic and patient specific advice on the assessment and management of AKI, with links to local guidance and points of specialist renal contact for advice. The AKI alert system developed here was named SAKI (Stop Acute Kidney Injury). As with any information technology (IT) solution though, the potential value of the clinical system will not be realised without use acceptance and adoption. In order to address this, a formal qualitative analysis of the use of the SAKI alert system at East Kent Hospitals University NHS Foundation Trust (EKHUFT) was performed to provide insight into and explanation of the processes involved in using an alert system in clinical care (Chapter 3). The study concluded that while the SAKI AKI alert system had significant benefits in terms of clinical intervention in acute kidney injury, and also the realisation of unexpected benefits such as the concept of education at the point of care, the study recognised a number of key areas that required improvement. The key areas included real-time delivery of AKI alerts, clear responsibility of care to be with the clinical teams with advice from the critical care outreach nurses and renal consultants as required, and improved communication with the clinical teams looking after the patients. From a user

experience point of view of the system, users required improvements in ease of use and accessibility of the system.

The next step in the quality improvement pathway was therefore to improve the usability and functionality of the alerting system in line with the issues raised in the qualitative analysis and importantly to deliver these alerts to the point of care in real-time and to the correct health care professional. In a development partnership with the company Doctor Communications Limited, the alerting platform "Careflow" was developed to provide real-time acute kidney injury (AKI) alerts to the clinical teams looking after the patients on their mobile devices, accessible anywhere. The system also re-aligns the clinical responsibility for acting upon the alert, ensuring the responsibility remains with the clinical team, a key requirement highlighted in the qualitative analysis of the use of the previous SAKI reporting system. Unlike other alerting and clinical systems, the "Careflow" platform also allows a clear transparency as to the viewing of alerts (with recorded and visible user views), with the additional ability to add clinical comments/communication directly to alerts, and in this way allow real-time clinical communication/collaboration around an alert, including with members of the specialist critical care outreach and renal teams. With an improved system in place, based on user level feedback, to provide real-time alerting of patients with acute kidney injury to the point of care, this will allow early intervention and management changes in those patients in order to improve outcomes and limit resultant complications and sequelae from AKI.

Following a clear definition of the epidemiology of AKI (Chapter 2) and the development of a system to provide clinical alerting of the presence of AKI to the point of care, the next stage in the quality improvement process was to go one step back in the disease process and focus on the ultimate form of treatment, namely prevention. By determining a patient's risk of AKI it should then be possible to define and ultimately alert (using the described "Careflow" alert system) to high-risk patients, in which simple interventions can be instigated to prevent the occurrence of AKI, or in patients who already have AKI, prevent worsening of the disease process, reducing resultant sequelae.

In the literature the majority of reports assessing risk of AKI and developing risk models focus on the need for renal replacement therapy (RRT) after cardiac surgery. One of the first of these was by Chertow *et al* who produced a risk model for predicting AKI after cardiac surgery, based on a population of 40,000 patients who underwent cardiac bypass or valvular surgery in 43 Veterans Administration Hospitals in Virginia. [211] A risk-stratification algorithm was formulated on the basis of interactions between potential risk factors. [211] There were inherent flaws in the study cohort, specifically a lack of females and African-American patients. Thakar *et al* produced a clinical risk score to predict post–cardiac surgery AKI requiring RRT, based on 33 217 patients who underwent cardiac surgery at the Cleveland Clinic between 1993 and 2002. [183] The scoring system was derived based on 13 preoperative factors which were weighted and the sum of the scores, ranging from 0 to 17, allowed for stratification of postoperative risk of AKI from low to high. The lowest-risk group (score 0-2) had a risk for AKI requiring RRT of 0.4%, in contrast to the high-risk stratum (score 9-13) who had a RRT risk of 21.5%. [183]

There is however a paucity in the literature of studies regarding the risk and risk prediction of AKI in unselected emergency admissions to a district general hospital. Finlay *et al* published a recent study of AKI risk factors associated with AKI in patients admitted to acute medical units (AMUs) in a study conducted over two separate 24-hour periods at a total of 10 AMUs. [212] Forni and colleagues have developed a model for predicting acute kidney injury in a subset of medical patients admitted to a UK hospital. [213]

The aim of the study reported here was to develop risk models for the development of acute kidney injury in a general hospital setting, in an unselected population. While risk models can be employed at any point during hospital admission, as data becomes available, as was clear from the qualitative analysis presented in Chapter 3 it is key that an alert of risk is delivered to the right person at the right time in order to inform and influence decision making and add value to a patient's care. It was determined therefore, that there were two

time points during a patient's admission where significant clinical decision making takes place, at which the use of risk models would have greatest impact on clinical care and patient management. These points (see Chapter 5, Figure 33) are firstly at the point of admission to hospital to guide renal function testing and inform admission planning, and secondly, at 24 hours after admission, often on the post-take ward round to highlight patients who are likely to develop new or worsening AKI if already present, in the first 72 hours of hospital admission so that appropriate management decisions can be made on the ward round.

The study here developed and assessed traditional methods to provide risk models for the prediction of new or worsening acute kidney injury (AKI) in patients presenting to hospital and in their management within the first twenty-four hours of admission. From the risk modelling presented here, a risk model has been developed (risk Model 1, Chapter 5) to predict patients who will have AKI at admission to hospital, and to guide renal function testing using this model along with the clinical practice algorithm. The Receiver Operating Characteristic (ROC) curve analyses suggest that there is discriminatory power of the model, and with an Area Under the Curve (AUC) value of 0.75 this is acceptable for use in clinical practice. This has been validated in a second population. This model was also re-defined with use of the NHS England algorithm (Appendix 9) to define AKI. The ROC curve analysis demonstrated an AUC of 0.73 with use of this definition of AKI.

A risk model has also been developed (risk Model 2, Chapter 5) to predict patients who will develop new AKI in the first 72 hours of admission to hospital. The ROC curve analyses suggest that there is discriminatory power of this second model but this is not as effective as the admission model, with an AUC value of 0.68. This has again been validated in a second population. This model was also re-defined with use of the NHS England algorithm (Appendix 9) to define AKI. The ROC curve analysis demonstrated an AUC of 0.67 with use of this definition of AKI. The third model to predict worsening AKI in the first 72 hours of hospital admission (risk Model 3, Chapter 5) did not prove to have any discriminatory power and would not provide clinical benefit. This was therefore

not validated further. From the modelling to predict worsening AKI in the first 72 hours of admission, these results suggest that key variables have not been included in the model or that the development of AKI in hospital is subject to a random effect, which is not measured. The model to predict new AKI in the first 72 hours may be refined further once physiological data becomes more commonly available electronically across the NHS.

The methodology used here has its limitations, which will be discussed further in Chapter 7 and further analysis and testing, including continuous modelling, non-linear modelling and interaction exploration may refine the model further. This study provides valuable evidence of the relationships between key variables available from hospital electronic records, and acute kidney injury. This work also gives other insights as to which variables may not be associated with AKI, something that has been lacking in the literature.

It is important that models developed here are generalisable and transferable across the National Health Service (NHS). Using a number of hospital databases combined the work here has identified a number of key variables which predict acute kidney injury (AKI). This methodology can therefore be used to highlight patients at risk of AKI. The findings have been validated in a second dataset from the same hospitals and then a further dataset from a second hospital trust with very different population characteristics. The key variables used in these models are available in most UK hospitals and the majority of them are not susceptible to coding bias, however the potential for such bias is always a concern.

During the course of the work present in this thesis a number of methods of alert delivery have been explored. NHS England has implemented alerts to the presence of AKI across the NHS however there are no plans to alert to risk of AKI. Desktop alerting systems can be easily made available across the NHS with little adaption of existing IT systems. The use of “push notification” to mobile devices may require infrastructure changes in some NHS hospitals; however, there has been a significant increase in the availability of wireless communication and mobile devices in recent years.

NHS England have recently made considerable progress in improving patient safety with respect to acute kidney injury. A national algorithm has been developed to standardise the definition of AKI. A patient safety alert was issued on 9th June 2014 requiring all hospital Trusts to embed the algorithm in routine pathology reporting. Whilst this will go a long way towards the identification of established acute kidney injury it does not address the issue of prevention of harm in the first place hence the requirement for the development of risk assessment tools a key recommendation of the NCEPOD report. [100] In addition the reporting of AKI will not require a response by the attending medical team in other words there is currently no requirement for a standardised response to alerts to established AKI.

The work reported here and a future study examining the impact of an automated alert will inform further national strategy with respect to AKI prevention. The work here and further studies examining the complexities of implementation of auditable clinical alerts have informed these workstreams and in the future will provide more clarity in a complex area.

To date there have been no intervention studies in comparable unselected populations which have shown a reduction in episodes of acute kidney injury. A formal health economic analysis of the impact and costs of such intervention needs to be performed along with technology appraisal to maximise the benefit from electronic alerting.

Conclusion

The work reported here has demonstrated the significant morbidity and mortality both long and short term of patients who experience acute kidney injury managed in hospital and has developed methods of alerting the presence of AKI to the point of care in real-time to ensure efficient intervention with an aim to improve these outcomes. Qualitative work has also highlighted the complexity regarding the implementation and delivery of alerting systems to the clinical front line. The work reported in this thesis has also demonstrated that

routinely available data can be used to highlight patients at risk of acute kidney injury both at the point of admission to hospital and following admission. However, the methodology used has its limitations and further analysis and testing, including continuous modelling, non-linear modelling and interaction exploration may refine the model further. The work here provides valuable evidence of the relationships between key variables available from hospital electronic records, and acute kidney injury. Some of the models may be refined further once physiological data becomes more commonly available across the NHS.

What this work adds

The work in this thesis has made a significant contribution to both the literature and national policy in the detection and management of acute kidney injury (AKI), and provides a firm basis for future work in both the fields of clinical alerting and risk assessment. Chapter 2 (and published in the academic literature – see Appendix 2: Paper 2: What is the real impact of acute kidney injury?), brought our understanding closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date. This work highlighted to both healthcare professionals and managers the importance of AKI in clinical practice both in terms of a clear understanding of morbidity and mortality and subsequent increased burden and cost to the healthcare economy, (see Appendix 3: Paper 3: The economic impact of acute kidney injury in England). These results have provided a baseline for quality improvement projects aimed at early identification, improved management and where possible prevention of AKI. The publication of these papers led to considerable debate within the media, the medical community, and at a high level within the Department of Health. Following this NHS England released a patient safety alert (Stage Three: Directive) mandating that all Trusts in England alert to AKI, and with this delivered a standardised algorithm for the detection of AKI (see Appendix 9).

Following this work the AKI National Programme developed the “Think Kidneys” quality improvement partnership to raise awareness of and improve the management of AKI.

After defining the true impact of AKI, and stimulating the debate within the medical community, the work here then progressed to methods of aiding the improvement of management in clinical practice. The work reported here has developed a simple reporting / alerting tool to define all patients within a hospital trust who have acute kidney injury (AKI), to allow focused and standardised clinical intervention by Critical Care Outreach Nurses and specialist Renal Consultants. Importantly the use of Critical Care Outreach Nurses to support the management of AKI has been replicated in numerous other NHS trusts throughout England following this work, and is currently being tested in a project supported by the National Institute for Health Research (NIHR). The work here also nurtured the idea of education at the point of care with Critical Care Outreach Nurses trained in the management of AKI providing education to healthcare professionals including junior doctors and nursing staff, while reviewing patients with AKI following the alert.

A qualitative study was performed to assess the integration of the alerting system into clinical care. While a small study this provided valuable insights into professional interactions, information sharing, and personal and professional characteristics on the use of electronic clinical information and clinical decision support. This work informed further developments in alerting to the point of care. The alerting development work here, as part of a development partnership with a commercial company, developed a new alert system to provide real-time alerting of patients with AKI to the point of care, utilising mobile device technology, and allowing collaboration with specialist teams in real-time. This successful system has now been implemented in a number of NHS trusts in England to provide AKI alerting as well as much wider reaching benefits including other patient safety alerts and for clinical communication, referrals and collaboration in real-time. Since this development a number of other companies have created similar systems including Google Deepmind.

The next step in this thesis was to move a back in the disease process to before AKI develops, and with risk assessment ultimately aim at prevention. This study provides valuable evidence of relationships between key variables and AKI and has developed a clinical algorithm and risk models for risk assessment within the first 24 hours of admission. This work provides a firm basis and direction in the literature to guide further risk model development in this area. The models were validated in the index population, a second demographically differing population, and re-validated with the use of the NHS England algorithm to define AKI and hence are generalisable and transferrable within the NHS.

The work in this thesis has set the stage for future work and clinical trials of both AKI and AKI risk alerting in clinical care, in terms of clinical benefit and cost effectiveness.

Chapter 7: Strengths and weaknesses – future work

The work described in this thesis is part of a quality improvement journey to begin to highlight and address the disease process of acute kidney injury (AKI) in clinical medicine within the secondary care (hospital) environment. Whilst the work here has provided valuable insights into the epidemiology, natural history in hospital, health care costs of the disease, methods of alerting clinicians and healthcare professionals as to the presence of the disease and finally to define key variables and develop risk models to determine risk of AKI, this work cannot purport to have defined an entire quality improvement program for AKI. There is now a national program of quality improvement for AKI (named: 'Think Kidneys'), which the work here both has, and will inform.

The epidemiological study presented in Chapter 2 is a population-based analysis, which considers all patients admitted in a general hospital setting in the United Kingdom during a 6-month period. The catchment population for this cohort is from East Kent in the South East Coast of England. In comparison to the wider population in England East Kent has an older population (mean age 42 years compared to the national mean age of 39) but with fewer ethnic minorities (6.3% of Black and Ethnic minority compared with 14.6% nationally). [105] Nevertheless, in this study the data linkages between the pathology, hospital data warehouse and renal systems enabled the work to come closer to the 'real' incidence and outcomes of AKI managed in-hospital than any study published in the literature to date.

This study is a retrospective database study and clearly has limitations. Key to the definition of AKI is knowledge of pre-morbid kidney function (baseline SCr) and the threshold value of SCr from which change is measured (reference SCr). The importance of baseline SCr is in the determination of pre-existing CKD and this value should be based on SCr values available > 3 months prior to the index event. The reference SCr should be ideally be the lowest SCr recorded within 90

days of the event to distinguish this value from the baseline SCr. However, practically in many cases there may be either few or no pre-hospitalisation SCr values making distinction between baseline and reference SCr impossible. This is an area that requires further guidance and consensus from the international community and various strategies have been suggested including varying the baseline/ reference creatinine from admission to 365 days prior, [95] taking the average of values between 7–365 days prior to admission,[96] back calculating reference SCr for missing values from an assumed MDRD glomerular filtration rate of 75 ml/min/1.73 m^2, [97] and (most recently) a method employing multiple imputation using known comorbidity strengthened by factoring in the lowest admission SCr. [98] For simplicity the lowest SCr in the 12 months prior to the acute rise was chosen to define AKI. It may be that by doing this the study has included patients with progressive CKD and defined them as AKI stage 1. However, as LaFrance et al. [95] demonstrated and the data here confirms, patients with AKI stage 1 using this methodology still have a significantly increased likelihood of a specific adverse outcome occurring compared to patients with no AKI.

The lowest serum creatinine in the 12 months following discharge was utilised to categorise AKI (for those without pre-hospitalisation creatinine) in 8.2% of admissions with AKI. It is acknowledged that the assumption that AKI was present if serum creatinine improved following admission by greater than 26.4 μmol/l may not always be correct but use of this methodology was only necessary in 8% of those categorised as having AKI. The incidence of AKI in admissions utilising a post discharge baseline (9.9%) was less than in those where pre-admission creatinine data was available (16.1%).

Since this population study was conducted NHS England has defined/developed a national algorithm to standardize the definition of AKI, and dictated the routine reporting of AKI in trusts in England, which will address a number of these issues. By standardization this will allow clear comparison of data reported from across England and the work conducted by the Renal Registry in partnership

with NHS England will allow the collection of AKI reporting from across the country, to add further clarity as to the 'true' incidence of AKI.

It is also not possible to be certain that none of the patients with insufficient SCr data experienced AKI. These patients were significantly younger and had less co-morbidity than those with sufficient SCr data and either had one or no SCr result prior to, or following hospital admission. Survivors (9,830 of 10,030) were also short stay patients (LOS 0–2 days) and were therefore unlikely to have sustained any degree of AKI. The 200 patients in this group who did not survive the hospital admission had a mean LOS of 13.5 days, lack of baseline SCr data precluded derivation of AKI status in these patients. This also raises the issue of possible ascertainment bias, that sicker patients may have more creatinine tests, increasing the probability of detecting AKI.

Co-morbidity data was extracted from the hospital data warehouse using validated algorithms, however this still relies on the accuracy of coding of clinical episodes, which may not necessarily be correct. This also applies to the analysis of increase in care on discharge, which relies on the accurate coding on the PAS at time of discharge.

While the statistical models used in this analysis have accounted for multiple confounders identified in the literature to date there is always the possibility that there may be other confounders hitherto unknown.

Finally, despite the estimates reported in this study of the incidence of AKI in a typical general hospital setting being the highest to date, EKHUFT does not provide cardiothoracic, liver or burns services and the reported incidence of AKI may still be an under-estimation of the total population incidence.

Following on from the epidemiology to define the problem of acute kidney injury, the next step in the work here was to develop alerting systems to alert healthcare professionals to the presence of AKI as soon as this information is available, aiding recognition and in doing so, start to improve its management.

The initial work here developed and implemented a reporting tool to define patients in hospital with AKI and then direct specialist intervention in terms of both critical care outreach and renal specialist services, to these patients. The qualitative analysis reported here has provided guidance as to the best approach to further implementation of clinical alerting in AKI, however, this is a small scale analysis in one centre and as such, may not be generalisable. The next step in development involved a partnership with a commercial company to provide real-time alerting of AKI to the point of care on mobile devices, accessible anywhere. Whilst this aims to alert to the presence of AKI to the clinical team looking after the patient the instant the known presence of AKI is available, a number of issues do need to be addressed in future work.

Firstly, to date there have been no intervention studies involving alerting systems for AKI reported in the literature that have shown clear clinically statistically significant benefit in terms of reducing AKI progression and improving outcomes in terms of morbidity and mortality. Secondly, there is no standardised method used to alert to AKI. Over the last 5-years methods of alert definition and delivery have been developed, often governed by resources available and logistic considerations at each hospital trust. While the patient safety directive from NHS England goes the first step to ensuring alerting occurs, it does not define a method of delivery of alerts. A future multi-centre study is required to test various methods of alert delivery to define the best method to adopt nationally to add clinical value to the patient's care, in terms of improving outcomes in AKI. One other issue previously with AKI alerting nationally has been the differing methods of defining baseline kidney function, however, this has been addressed with the NHS England national algorithm for AKI as described.

In terms of generalizability the resources of each NHS trust must be a determinant factor in AKI alerting delivery. Whilst some trusts may have full coverage of wireless services with an extensive wireless network and all junior and senior doctors and specialist nurses having trust mobile devices, others may be technologically far behind this position, especially in the current financial

climate. This does suggest, however, that a health technology assessment is required in this area to ensure such systems can deliver clinical cost effectiveness. It also raises a question of a bring your own device (BYOD) policy within the NHS, as most healthcare professionals own a mobile device/smartphone that can provide this technology, however this raises further issues of security, standardisation, and the use of personal devices for working.

The next step in the work described here moved one stage back in the disease process of AKI to the ultimate form of treatment, namely prevention. In the AKI risk modelling analysis presented here to develop risk models to predict AKI on admission to hospital and at 72 hours into the hospital admission, the weaknesses of this study include the fact that this was a retrospective cohort study using hospital databases to find predictors of acute kidney injury. It was carried out in a small geographical area of England (Kent) and covered a one-year period. Neither of the hospitals studied have cardiothoracic services. The combination of such a dataset is labour intensive and as such would not provide generalizable results unless an easily accessible sub-set of the data were found to be useful predictors. The work here has provided a list of candidate variables for the prediction of acute kidney injury at admission and 72 hours. Importantly, the work has also provided a comprehensive analysis of variables that do not appear to influence the risk of acute kidney injury. The modelling techniques used here have been unable to produce a predictive model for worsening acute kidney injury during admission. This may be because key candidate variables have not been included or that it is due to a random effect.

In future work, further analysis and testing, including continuous modelling, non-linear modelling and interaction exploration may refine the models further. Certain groups of patients were excluded from the analysis (for example those with established AKI) requiring the use of a clinical practice algorithm as well as multiple predictive models for use in different scenarios.

However, the study reported here used a very large unselected dataset, which represents the kind of populations presenting to the majority of UK hospitals.

Whilst there was no cardiothoracic surgery performed at either hospital, AKI in this setting has been extensively studied and represents a very small and unrepresentative group of people with AKI. The study was carried out using robust methodology, the initial dataset used to develop the models was randomly selected from all hospital admissions over a year on a 3:1 ratio. The model was validated in the remainder of the population and then subsequently tested in a second population from a different hospital trust demonstrating that ethnic and social differences had little effect on the models, neither did the potential difference in coding practices between organisations. The work here has therefore been able to demonstrate that these models can transfer to another hospital trust, however these models may only provide a platform for further analysis and refinement before they can be employed more widely. This should be the basis of future work to both provide accurate modelling for AKI across the NHS and in the form of a randomised controlled trial assess the effects of alerting to this risk in the clinical management of a patient.

Ultimately a health technology assessment is required of both AKI and AKI risk alerting in clinical care, in terms of clinical benefit and cost effectiveness. In future work another important consideration is the use of AKI as a clinical warning method. It has been suggested that in many cases AKI is not a specific sole disease process but is more of a marker of general clinical deterioration of a patient as part of a multi-system/organ involvement of another disease process. In this light, future work should look at the interaction between AKI and clinical alerting systems such as the National Early Warning Score (NEWS) and definitions of SIRS (systemic inflammatory response systems) and more importantly sepsis.

The National AKI program is aimed at addressing a number of the above, unanswered questions and providing standardisation of definition and clinical assessment and care in this disease. However, this guidance must have a clear evidence base and this must be the core of future work in acute kidney injury.

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Appendices

Appendix 1: Paper 1: Acute Kidney Injury and CKD: Chicken or Egg?

AJKD
Editorial

Acute Kidney Injury and CKD: Chicken or Egg?

Recent longitudinal cohort studies have suggested that episodes of acute kidney injury (AKI) with only small transient decreases in kidney function are associated with the subsequent development of chronic kidney disease (CKD).[1-6] Both CKD and, more recently, AKI are well recognized as global public health issues, associated with significant morbidity and mortality and resultant health care economic burden. There is considerable conceptual overlap and interplay between the underlying pathophysiology and pathology, definition, risk factors, and outcome of the 2 conditions. Do silent and unrecognized episodes of AKI precede the development of CKD and hasten its progression?

Is There a Common Underlying Pathophysiologic Pathway?

Determining the pathophysiology and pathology underlying acute kidney disease and CKD helps us understand their conceptual overlap and how to accurately detect and define them. Changes in renal vasculature occur with age, as in other vascular beds, often due to comorbid conditions, but also in their absence.[7] It is suggested that these changes eventually cause cortical glomerulosclerosis, interstitial fibrosis and tubular atrophy, and compensatory hypertrophy and hyperfiltration of glomeruli in the medulla, contributing to CKD development.[8] It also has been suggested that low birth weight is associated with subsequent CKD through low nephron number and compensatory hypertrophy and hyperfiltration of glomeruli.[9] With increasing age and CKD, function in both proximal and distal tubules is compromised, hampering the ability to control fluid and electrolyte balance and affecting tubuloglomerular feedback.[7,10] These changes may exacerbate clinical events such as dehydration and drug toxicity, which carry a high risk of AKI.[8] Given that people with CKD have an increased burden of vascular disease, they may be more susceptible to ischemic AKI. Supportive data from animal models suggest AKI as a "vasomotor nephropathy,"[11,12] but what happens after AKI? Renal tissue has the ability to recover from sublethal or lethal cellular damage.[13-17] However, function may not be fully restored, with the development of CKD.[14] Kidney function may be related directly to a cycle of cell injury and recovery after AKI (Fig 1A).[18] Damage to renal tubular epithelial cells is thought to be extended by renal vascular endothelial injury and dysfunction. Endothelial repair is important to overall recovery and thus may have an impact on long-term function.[19] This model describing cellular phases of AKI applies to acute tubular necrosis, but can be extrapolated to other causes of AKI. What happens most frequently is limited to the very early part of this process. In patients developing CKD (Fig 1B), the initiating insult leading to damage, inflammation, and repair (initiation) may result in fibrosis (extension) and then further damage in a self-perpetuating cycle of progression (maintenance) to end-stage renal disease (ESRD). Early intervention at the stages of initiation and extension may prevent CKD and ESRD, whereas later intervention during the maintenance stage may only delay progression, with the extent of delay determined by the success or otherwise of intervention. Patients with AKI may or may not have pre-existing CKD (Fig 1C). Okusa et al[20] (pathophysiologic concepts from Sutton et al[18]) suggest that after AKI, there are 4 possible outcomes: (1) full recovery, (2) incomplete recovery resulting in CKD, (3) exacerbation of pre-existing CKD accelerating progression to ESRD, and (4) nonrecovery of function leading to ESRD. AKI also may recover incompletely, leading to a step down in glomerular filtration rate (GFR) falling short of CKD. Patients with AKI are also likely to have risk factors for CKD; thus, patients without known background CKD who develop AKI may already have unrecognized kidney disease and decreased functional reserve, not yet manifest as CKD. These patients are programmed to develop future CKD, and the AKI episode simply speeds up the development of overt CKD. In this respect, renal outcomes of AKI and CKD are the same, suggesting they are part of the same pathophysiologic pathway.

A key question is whether the "I" in AKI truly stands for injury or for impairment and/or injury. Is it underpinned by histopathologic damage and, if so, when does this become relevant in terms of future CKD and/or progression? Do undetected episodes of AKI in the community lead to CKD? When patients present with CKD without an obvious cause, is the pathophysiology related to multiple undetected AKI events in the community?

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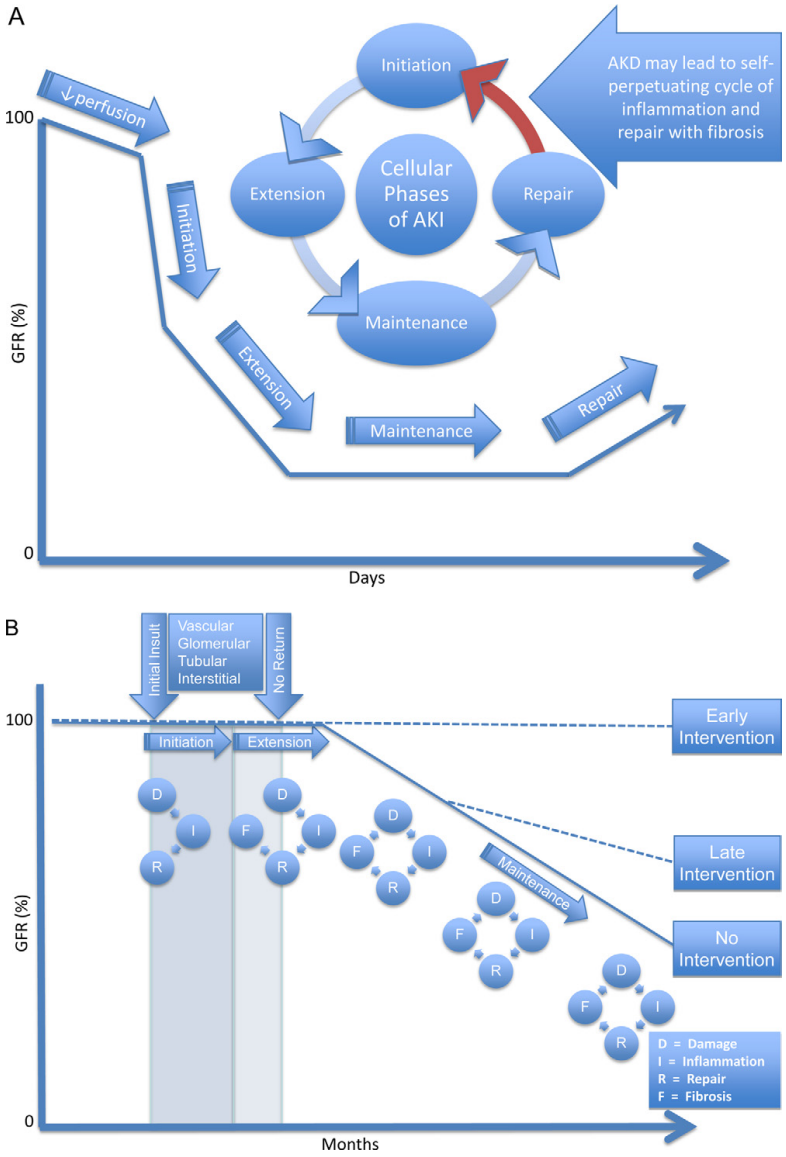


Figure 1. Conceptual model of glomerular filtration rate (GFR) and cellular pathology over time in acute kidney injury (AKI), chronic kidney disease (CKD), and AKI and CKD. (A) The cellular phases of AKI leading to repair, highlighting the possibility of initiating a self-perpetuating cycle of inflammation producing fibrosis leading to CKD. (B) The phases of cellular injury in CKD. After an initial insult, there is initiation of the inflammatory response with repair. This then may lead to the extension phase with added fibrosis. Past a point of no return, the disease process embarks on a self-perpetuating cycle of cellular damage and fibrosis (maintenance phase) leading to deterioration in GFR and progression to end-stage renal disease. The figure also shows the effect of intervention on the disease process. (C) The effect of episodes of AKI on the progression of CKD with 3 possible outcomes; complete recovery, stepwise progression, and inexorable decline.

From an ischemia-reperfusion injury model of AKI in rats, Basile et al[19] hypothesized that as long as there is adequate functional reserve, the single-nephron GFR of surviving nephrons increases to maintain a constant total GFR. This suggests that even in patients in whom creatinine and GFR values return to base-

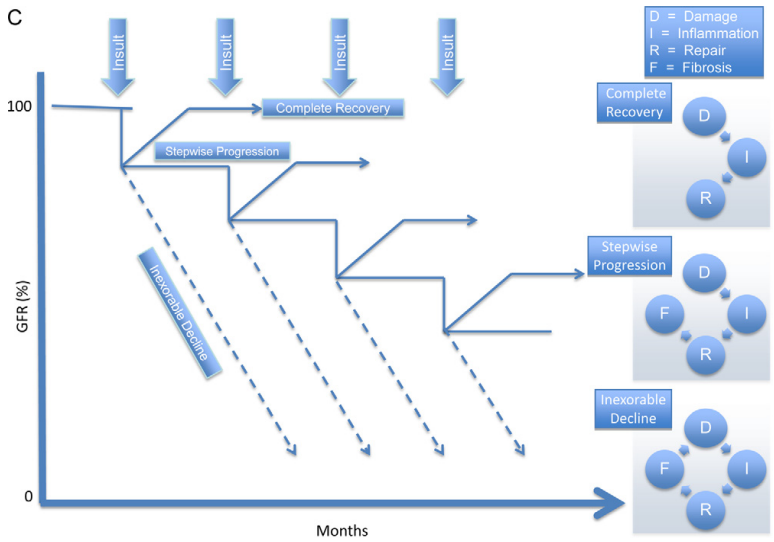


Figure 1. (Continued)

line, there may be underlying permanent damage masked by compensatory mechanisms. These patients subsequently may have an increased risk of CKD and AKI due to underlying "subclinical" damage.

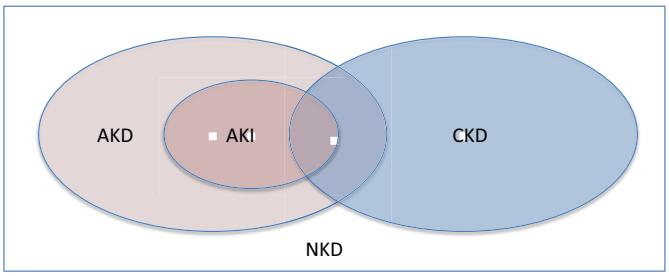
Are AKI and CKD biologically part of the same pathologic pathway with eventual glomerulosclerosis and interstitial fibrosis, with AKI leading to fibrosis by setting up the cycle of inflammation and cell repair?

Translation From Pathophysiology and Pathology to Clinical Practice and a Clinical Definition

The difficulty comes with the necessary time constraints. For AKI, there must be an increase in serum creatinine level over 2 (Acute Kidney Injury Network [AKIN] criteria[21]) to 7 (RIFLE classification[22]) days. For CKD to exist, GFR must be decreased or there must be evidence of kidney damage for at least 3 months.[23-25] These definitions may not capture all cases of acute kidney disease. Certain causes may lead to changes in serum creatinine and GFR values during a time outside those currently specified, precluding definition. These cases should not be neglected because intervention may be required. For this reason, the new KDIGO (Kidney Disease: Improving Global Outcomes) AKI guideline proposes an operational definition for acute kidney diseases and disorders (AKDs), of which AKI is a part, and provides a diagnostic algorithm for defining AKD, AKI, and CKD (Fig 2).[26]

Accurate definition has important research implications. Previously, variation in definitions used and populations studied made determination of epidemiology and the interplay between AKI and CKD more difficult. This has been improved by adoption of the RIFLE and AKIN classifications of AKI. However, problems arise when baseline creatinine level is not known. A retrospective cohort study by LaFrance and Miller[27] assessed 1,126,636 veterans (US Department of Veterans Affairs health care system) hospitalized at least once between 2000 and 2005. The highest serum creatinine level during hospitalization was compared with the lowest using 4 different baseline periods (in-hospital only and 3, 6, or 12 months preadmission). AKI was defined as a greater than 1.5-fold increase in serum creatinine level or an increase of 0.3-0.5 mg/dL over baseline.[27] The cumulative incidence of AKI ranged from 12.5% (in-hospital baseline) to 18.3% (baseline up to 12 months preadmission). By extending the baseline period to at least 3 months, they found that discriminative power increased slightly (C statistic increased from 0.846 to 0.855; $P = 0.001$). They suggested a need for consensus on defining baseline in database studies. The KDIGO AKI guideline suggests that an estimated creatinine level can be used provided there is no evidence of CKD.[26] However, there are cases of CKD in the community not previously appreciated. Estimating baseline creatinine level in these cases may lead to the diagnosis of AKI in patients with previously unrecognized CKD.

Definitions of both AKI and CKD in the literature may not be accurate or comparable. For example, the



	Functional Criteria	Structural Criteria
AKI (acute kidney injury)	Increase in SCr by 50% within 7 days, *or* increase in SCr by 0.3 mg/dL within 2 days, *or* oliguria	No criteria
CKD (chronic kidney disease)	GFR <60 for >3 mo	Kidney damage for >3 mo
AKD (acute kidney diseases and disorders)	AKI, or GFR <60 for <3 mo, *or* decrease in GFR by ≥35% *or* increase in SCr by >50% for <3 mo	Kidney damage for <3 mo
NKD (no known kidney disease)	GFR ≥60, stable SCr	No kidney damage

Figure 2. Definitions of kidney disease and their overlapping relationship. Estimated glomerular filtration rate (GFR [mL/min/1.73 m^2] assessed from measured or estimated GFR) does not reflect measured GFR as accurately in acute kidney injury (AKI) as in chronic kidney disease (CKD). Abbreviation: SCr, serum creatinine. Adapted from the KDIGO (Kidney Disease: Improving Global Outcomes) AKI guidelines,[26] with permission of KDIGO.

definition of CKD based on diagnostic coding or preoperative GFR taken as baseline function can introduce bias in detection. Singh et al[28] suggested that differences also could reflect greater specificity of administrative codes for AKI in patients without CKD. This emphasizes the need for consensus about the definition of baseline function.

By defining AKI and CKD, we are describing decreased function, which can lead to complications including ESRD and mortality. In disease prevention/detection, we therefore aim for risk modification. There clearly is a significant overlap in risk factors for AKI and CKD. Elderly patients have a higher prevalence of AKI and CKD related to an increased prevalence of comorbid conditions (hypertension, diabetes, atherosclerotic disease, and cardiac insufficiency).[29] This is at least partly due to an increased prevalence of comorbid conditions with age. With common risk factors that may be playing a pathophysiologic role, the entities of AKI and CKD may be a process of definition of the same pathophysiologic pathway. The significant overlap in risk factors also makes investigation of CKD as a risk factor for AKI, and the converse, difficult. Is it possible to accurately correct for all confounding variables?

Are CKD and AKI Risk Factors for Each Other?

The literature suggests that CKD is a significant risk factor in the development of AKI.[1,30-34] In a number of studies, after multivariate adjustment for comorbid conditions, CKD consistently remains an independent risk factor for AKI after radiocontrast administration, cardiac surgery, and sepsis.[35] Table 1 lists evidence from the literature showing overrepresentation of CKD in the population that develops AKI, suggesting that CKD is a risk factor for AKI. There also is mounting evidence that AKI is a risk factor for or, more accurately, "contributes" significantly to CKD and CKD progression, leading to ESRD (Table 1). Hsu et al[41] suggested that the growth of ESRD incidence in the United States could not be accounted for solely by an increase in CKD incidence and may be attributable in part to AKI. A population-based study by Ali et al[42] compared patients with acute on chronic kidney disease with those with AKI alone. Patients with acute-chronic kidney disease were older, with less chance of renal recovery.[42]

Is part of the increased risk of AKI in patients with background CKD the fact that they are heavily burdened with comorbid conditions, as a result of which they are more likely to experience nephrotoxic insults such as radiocontrast nephropathy? The CKD population also is more likely to be using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics, increasing susceptibility to AKI. This population is more likely to have kidney function tested and AKI discovered. Conversely, patients without pre-existing CKD have fewer comorbid conditions, are less likely to be using susceptibility agents, and are less likely to have kidney function checked; hence, AKI (especially milder stages) may remain undiscovered. We suggest that these "silent and discrete" episodes of AKI in the community may relate to CKD development and progression. However, data are lacking in the literature and this requires further investigation.

What Is the Effect of AKI and CKD on Outcome? Is It Summative?

In terms of nonrenal outcomes, there is clear evidence that outcome from AKI is poor. From local data, only 56% of patients who experienced severe

Table 1. The Association Between CKD and AKI From the Literature

Study	Population	Conclusions
	CKD as a Risk Factor for AKI	
Nash et al,[36] 2002	Consecutive medical and surgical admissions of an urban tertiary-care hospital; N = 4,622	7.2% developed AKI, of which 45.5% had baseline SCr >1.2 mg/dL
Chertow et al,[37] 2006	618 ITU patients with ARF; data from PICARD	32% of patient with ARF had baseline GFR <30
Hsu et al,[38] 2008	1,746 AKI patients requiring dialysis compared with 600,820 hospitalized patients who did not develop AKI	ORs for developing AKI, by GFR: GFR >60, 1.00 (reference) GFR 45-59, 1.95 GFR 30-44, 3.54 GFR 15-29, 28.5 GFR <15, 40.07
LaFrance et al,[39] 2010	CKD population with GFR ≤30	44% had a least one episode of AKI over a median of 19.4-mo follow-up
James et al,[40] 2010	920,985 adults with ≥1 outpatient SCr	Risk of admission with AKI increased with heavier proteinuria and decreased GFR
	AKI as a Risk Factor for CKD	
Ishani et al,[1] 2009	233,803 patients hospitalized in 2000, aged ≥67 y on discharge; did not have previous ESRD or AKI	Of patients with AKI and no background CKD, 72.1% had CKD documented within 2 y of AKI
Triverio et al,[2] 2009	89 patients requiring RRT on ITU	After AKI, 50% of patients without background CKD progressed to CKD within 3 y
Mehta et al,[3] 2004	618 ITU patients with ARF; data from PICARD	In-hospital mortality rate, 37%; rate of mortality or nonrecovery of kidney function, 50%
Mehta et al,[4] 2002	552 ITU patients with ARF	Of 258 patients who survived (47%), 17 (7%) were dialysis dependent after discharge

Note: Conversion factor for SCr in mg/mL to μmol/L, ×88.4; GFR given in mL/min/1.73 m^2 (for conversion to mL/s/1.73 m^2, ×0.01667).

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; ITU; intensive treatment unit; OR, odds ratio; PICARD, Program to Improve Care in Acute Renal Disease; RRT, renal replacement therapy; SCr, serum creatinine.

AKI in the hospital survived to discharge; only 28% survived to 3 years post discharge.[43] Most studies of AKI in the intensive care unit report mortality >50%. Intensive care unit and in-hospital mortality increase as the severity of AKI increases.[3,34,36,42,44-52] Even small isolated increases in serum creatinine level have an associated increase in short-term morbidity and mortality and longer term outcomes, including 1-year mortality.[3,34,44,53-57] However, could it be that AKI is not a risk factor for these outcomes, but is a risk marker of systemic illness? We know that isolated AKI without other organ involvement has a better prognosis than AKI in the context of multiorgan failure.

CKD also has been shown as an independent predictor of morbidity and mortality.[58,59] We therefore would assume that AKI in CKD has a summative effect on outcome. Studies show lower in-hospital mortality in patients with AKI on a background of CKD compared with patients without a background of CKD.[35,37,49,60-63] This would seem counterintuitive. One explanation might be that patients with CKD require less of an insult to manifest clinically apparent AKI or are more likely to have their kidney function tested and AKI discovered; thus, severity of the AKI episode is less in these patients with CKD and hence outcomes are better. Conversely, those with CKD may have more resilience to acute insults secondary to conditioning or priming and tolerate AKI better. It is also possible that those with CKD receive better/different care than non-CKD counterparts when AKI is identified, thus affecting outcomes. It also has been suggested that results may be confounded by malnutrition (lower serum creatinine values from low muscle mass).[50]

Conclusion

To conclude, both AKI and CKD confer significant morbidity and mortality. Regardless of which is the chicken or the egg, the risk factors and pathophysiology underlying AKI and CKD are similar. Should we consider AKI and CKD as part of the same pathologic pathway and a continuum over time and surmise, based on a 2-hit theory, that AKI before the diagnosis of CKD contributes to CKD and that AKI after the diagnosis of CKD exacerbates it? With an ageing population and increasing comorbidity burden, AKI and CKD will continue to have a significant impact on

health care economies. It is important that further effort is focused on improving the definition, diagnosis, effective prevention, and treatment of both conditions. Better understanding of this complex interplay will allow us to achieve this.

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Appendix 2: Paper 2: What is the real impact of acute kidney injury?

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RESEARCH ARTICLE Open Access

What is the real impact of acute kidney injury?

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Abstract

Background: Acute kidney injury (AKI) is a common clinical problem. Studies have documented the incidence of AKI in a variety of populations but to date we do not believe the real incidence of AKI has been accurately documented in a district general hospital setting.
The aim here was to describe the detected incidence of AKI in a typical general hospital setting in an unselected population, and describe associated short and long-term outcomes.

Methods: A retrospective observational database study from secondary care in East Kent (adult catchment population of 582,300). All adult patients (18 years or over) admitted between 1st February 2009 and 31st July 2009, were included. Patients receiving chronic renal replacement therapy (RRT), maternity and day case admissions were excluded. AKI was defined by the acute kidney injury network (AKIN) criteria. A time dependent risk analysis with logistic regression and Cox regression was used for the analysis of in-hospital mortality and survival.

Results: The incidence of AKI in the 6 month period was 15,325 pmp/yr (adults) (69% AKIN1, 18% AKIN2 and 13% AKIN3). In-hospital mortality, length of stay and ITU utilisation all increased with severity of AKI. Patients with AKI had an increase in care on discharge and an increase in hospital readmission within 30 days.

Conclusions: This data comes closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date. Fifteen percent of all admissions sustained an episode of AKI with increased subsequent short and long term morbidity and mortality, even in those with AKIN1. This confers an increased burden and cost to the healthcare economy, which can now be quantified. These results will furnish a baseline for quality improvement projects aimed at early identification, improved management, and where possible prevention, of AKI.

Keywords: AKI, Incidence, Impact, Outcomes, General hospital

Background

Acute kidney injury (AKI) is a common clinical problem characterised by an abrupt decline in kidney function, ranging from a small rise in serum creatinine (SCr) to anuric kidney failure requiring renal replacement therapy (RRT). AKI may either be present on admission to hospital, or develop during the course of admission. The many aetiologies and risk factors for AKI are well described [1-4], as are the short and long term consequences [1,2,4-7].

In the last decade the definition of AKI has been standardised, refined and adopted in clinical research [6,8] leading to improved understanding of the epidemiology of AKI and a realisation of its potential health economics impact [9].

A number of studies have documented the incidence of AKI in a variety of populations [9-20] but to date we do not believe that the real incidence of AKI has been accurately documented in a district general hospital setting. The aims of this study were therefore to (i) use the acute kidney injury network (AKIN) definition to describe the real incidence of AKI in a typical general hospital setting in an unselected patient population, (ii) describe the associated short and long-term outcomes, (iii) describe the health and social care consequences of AKI.

Methods

Patient population

Ethical approval for this study was obtained from Kent Research Ethics Committee (ref 10/H1101/89). All adult

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patients (18 years or over) admitted to East Kent Hospitals University NHS Foundation Trust (EKHUFT) between 1st February and 31st July 2009 were included. Time of entry to the cohort was the date of admission for each patient. EKHUFT comprises 3 general hospitals with a total of 1250 inpatients beds serving a defined population of approximately 744,400 people (582,300 adults) in the geographical area of East Kent in the southeast peninsula of England [21]. Patients were followed up until the 31st March 2011. Patients receiving chronic renal replacement therapy (RRT) (including dialysis and renal transplantation), maternity admissions and day case admissions were excluded from the analyses.

Data extraction

Data were extracted from the EKHUFT data warehouse. This data warehouse stores patient demographics and all patient episodes, including primary diagnosis and co-morbidity for each episode. Unique patient identifiers were used to link the data warehouse with the pathology database.

AKI was defined by the AKIN criteria using the lowest SCr in the 12 months prior to the date of hospital admission as the reference after the method of Lafrance et al. [22]. In cases where there were no pre-hospitalisation values and the follow up SCr (lowest in the 12 months following discharge) was lower than the peak in the study admission, the follow up creatinine was used as the reference SCr. The assumption was made that if SCr had improved following admission by greater than 26.4 μmol/L, then the admission must have involved an AKI (UK Renal Association, Acute Kidney Injury Clinical Practice Guideline) [23].

The peak creatinine during the inpatient stay was used to define the stage of AKI.

Independent variables

Patient demographics (to determine age and eGFR calculations), postcode (to determine deprivation score), co-morbidity, and primary diagnosis were extracted. Both co-morbidity and primary diagnosis were coded for each hospital episode on the data warehouse using ICD-10 codes. For primary diagnoses the ICD-10 group was extracted for each admission (Additional file 1: Table S1). For co-morbidity (secondary diagnoses), validated coding algorithms from Quan et al., [24] with further validated algorithms for diabetes [25] and hypertension, were used to determine a modified Charlson co-morbidity score for each patient. The number of admissions and outpatient appointments in the 12 months prior to a patient admission were also recorded. From the baseline pathology data, the baseline chronic kidney disease (CKD) stage was defined for each patient, using the baseline creatinine (lowest creatinine in the 12 months prior to admission), or the post-discharge nadir creatinine was used for the subset of patients without a pre-hospitalisation creatinine.

Outcomes

Mortality, hospital length of stay (LOS), intensive care LOS, and change in residence resulting from admission were recorded. Date of death and 30 day re-admission rates were also recorded wherever relevant. The date of death was obtained from the Patient Master Index (PMI) on the hospital patient administration system (PAS). Where a patient died in hospital this field was populated using the discharge details of the patient's episode and was therefore validated at the point the patient was discharged as 'died in hospital'. Where a patient died following discharge the PAS PMI record was updated via a weekly report from the Open Exeter national system which provides the date of death for any patient recently deceased [26]. Data on LOS, intensive care LOS, re-admission, and place of discharge were complete, as recorded on the hospital PAS.

All admissions during the recruitment and follow up periods were extracted. AKI stage was calculated for all admissions until the end of the follow up in order to inform the survival analysis.

Data were also extracted from the renal data system (Renal Plus, CHI) and from the intensive care database to determine whether patients in this cohort received RRT during admission, and whether they were still dependent on RRT 90 days post discharge. Patients who received RRT (often in ITU) but did not meet the creatinine criteria for AKIN 3, were upgraded to AKIN 3 in line with the specifications of the AKIN criteria.

Statistical methods

Patient level demographic summaries were performed, considering a single observation per patient. For patients with more than one admission with AKI data were summarised at the time of the admission with their highest AKI stage where there was a valid reference SCr. For patients who had no valid AKI recordings over the course of the study, data from the first admission was used in the analysis.

Normally distributed data were summarised as the mean and standard deviation. Continuous data not normally distributed were summarised by median and inter-quartile range, or the percentage of values in each category for categorical variables.

Three of the continuous variables, Charlson co-morbidity score, number of previous admissions in the previous 12 months, and number of outpatient appointments in the previous 12 months all had a very highly skewed distribution. So that outlying values were not overly influential, these three variables were categorised for analysis.

Chosen outcomes of interest were mortality, LOS, intensive therapy unit (ITU) utilisation, and increase in care following discharge. Regression analyses were performed to determine the impact of AKI on each outcome. Variables used in the regression model, and thought to be confounders were age, gender, primary diagnosis, modified Charlson co-morbidity score, stage of chronic kidney disease (CKD). We also added admission from residential or nursing care, deprivation index, hospital admissions and outpatient appointments in the last 12 months. The analyses were performed in three stages. In the first analysis, the effect of AKI upon each outcome was examined (an unadjusted analysis). The second analysis was age and gender adjusted and the third analysis was multiply adjusted, including the above variables.

For primary diagnosis in the regression model, specifically for elective admissions there were diagnosis groups with too few events. Therefore elective admissions were set as the reference and emergency admissions split by ICD-10 group for primary diagnosis.

Logistic regression was used for the analysis of in-hospital mortality and Cox regression for survival analysis. A time dependent risk analysis for survival was employed to allow adjustment for multiple admissions during the study and follow up period.

Analysis of LOS, which was highly skewed, was performed using negative binomial regression. The analysis of LOS was performed at the admission level in the recruitment period, and hence patients may have contributed to the analysis several times during the recruitment period. To allow for the correlation between repeat LOS values from the same patients a multilevel approach was employed, equivalent to fitting a random-effects model for subjects in addition to the fixed effects model.

In order to assess the social impact of AKI the change in residence related to the admission was assessed. An increase in care from home prior to admission to hospital, to residential or nursing care on discharge, was classified as an increase in care on discharge. This assessment was performed by stage of AKI.

Results

Population characteristics and AKI

During the 6 month recruitment period there were 66,829 admissions in 45,621 adult patients (Figure 1). After exclusion of maternity and day case admissions there were 36,015 admissions in 27,436 patients (79.1% of patients had 1 admission during the 6 month recruitment, 14.6% had 2 admissions, 4.1% had 3 and 2.2% had 4 or more). Overall, there were 10,030 admissions in 7,496 patients with insufficient SCr data to define AKI. Of these 42.9% were elective admissions and 57.1% were non-elective, the majority had a LOS of 0–2 days (see below). There were 20,464 admissions with no AKI and 5,521 admissions with AKI (8.8% of all admissions and 15.3% of non-maternity and non-day case admissions). Of these, 3,961 admissions had AKIN 1, 927 admissions AKIN 2, and 633 admissions AKIN 3. Of the 5,521 admissions with AKI, 4064 had AKI on admission (73.6%) and 531 of 633 admissions with AKIN 3 (83.9%) had AKI on admission.

Of the 36,015 admissions, baseline creatinine data in the 12 months prior to admission was available in 31,435 (87%). In the remaining 4,580 admissions the lowest creatinine in the 12 months following discharge (in survivors)

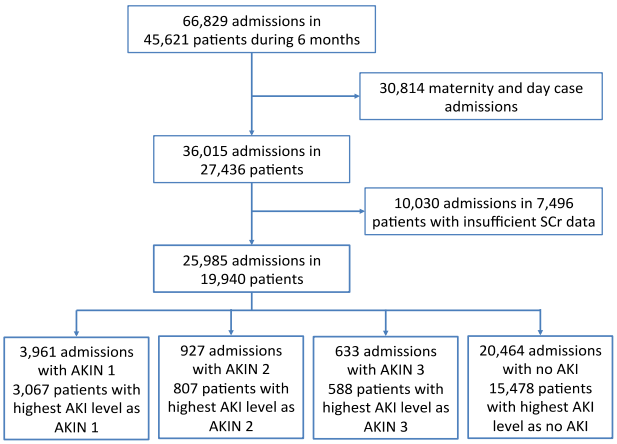

Figure 1 Derivation of the study population.

was used as the baseline serum creatinine. In these 4,580 admissions, 7.2% had AKIN 1, 1.4% AKIN 2 and 1.3% AKIN 3. This is in comparison to admissions in which a baseline from the 12 months following discharge was not used, in which 11.5% had AKIN 1, 2.7% AKIN 2 and 1.8% AKIN 3. In admissions culminating in mortality baseline creatinine data was obtainable in 1209/1379 (88%).

Overall, only 455/5521 admissions with AKI (8.2%) involved the calculation of a baseline using the lowest creatinine in the 12 months following discharge.

For descriptive statistics patients without sufficient SCr data ("no AKI info") are reported in the results but only those patients with valid SCr data sufficient to define AKI were included in the regression analyses. Patients with insufficient data to define AKI were younger, had less co-morbidity and shorter LOS than other patients (Tables 1 and 2).

The crude incidence of AKI in the 6 month period was 3,067 patients with AKIN 1, 807 AKIN 2, and 588 AKIN 3. In total, 4,462 patients from a catchment population of approximately 582,300 adults experienced AKI during the 6 month recruitment period, assuming the same incidence for the remaining 6 months of the year from a population of 582,300 this represents an incidence of 15,325 per million (adult) population per year (pmp/yr).

Co-morbidity as evidenced by the Charlson co-morbidity score was over represented in patients with AKI, and increased with AKI stage (Table 1). Deprivation was not related to AKI stage.

Renal Replacement Therapy (RRT)

Only 77 patients of the 588 patients with AKIN 3 (13.1%) received RRT. Of these, 16 remained on RRT 90 days following discharge (2.7% of AKIN 3). A further 4 patients who experienced AKIN 3 in their index admission (admission with highest AKI stage during the recruitment period) who did not require RRT during that admission, subsequently required chronic RRT within 90 days of discharge. There were also 2 patients with AKIN 1, 2 patients with AKIN 2 and 1 patient with no AKI info who did not require RRT in the index admission but subsequently required chronic RRT within 90 days of discharge. In total 25 patients were on chronic RRT at 90 days.

Survival analyses

Throughout follow up survival was related to AKI stage, (Table 3, Figure 2). In the upgraded risk analysis, after 12 months 92% of patients who had no AKI were still alive, in comparison to 28% of patients who experienced AKIN 3 (Figure 2).

Increasing severity of AKI was associated with increased risk of death and shorter survival even after multiple adjustment, AKIN 1 almost doubling the risk of death and AKIN 2 and 3 increasing the risk of death almost 3.8-fold and 5.5-fold respectively compared to those with no AKI (Table 4).

In-hospital mortality

Overall, 1,379 (3.8%) of 36,015 hospital admissions in the recruitment period resulted in an in-hospital mortality.

Only 2.0% of patients without AKI died in hospital compared with 8.1%, 25.6% and 33.3% of patients with AKIN 1, 2 and 3 respectively. AKI severity was significantly associated with in-hospital mortality even after multiple adjustment, the likelihood of mortality increasing 2.4 fold with AKIN 1 and 12 and 26 fold with AKIN 2 and 3 respectively compared to patients with no AKI (Table 4).

Length of stay

In those patients who died in hospital LOS prior to death averaged 10.0-13.5 days irrespective of AKI (Table 2). In those surviving to leave hospital LOS was associated with severity of AKI, ranging from a mean LOS of 4.4 days in patients without AKI, to 17.2 days in patients with AKIN 3. Compared to those with no AKI after multiple adjustment LOS was 1.5, 1.9 and 2.2-fold greater in those with AKIN 1, AKIN 2 and AKIN 3 respectively (Table 4).

Intensive Therapy Unit (ITU) utilisation

ITU utilisation increased with increasing AKI severity; 3.9%, 6.8% and 21.6% of patients with AKIN 1, 2 and 3 respectively were admitted to ITU, compared with 1.8% of patients without AKI. Intensive care LOS also increased with severity of AKI from a mean of 3.0 (SD 7.0) days in patients without AKI, to 4.4 (SD 7.8), 4.5 (5.4) and 7.3 (8.0) days in patients with AKIN stage 1, 2 and 3 respectively. After multiple adjustment, AKI severity was again associated with ITU utilisation. Patients were 2.8, 6 and 22 fold more likely to be transferred to ITU with AKIN stage 1, 2 and 3 respectively compared to patients without AKI. In patients who went to ITU their length of stay in ITU was 37%, 35%, and 111% longer in patients with AKIN stage 1,2 and 3 respectively compared to patients without AKI.

Increase in care

A greater proportion of patients with AKI (4.5% AKIN 1, 5.7% AKIN 2 and 3.7% AKIN 3) had an increase in care on discharge in comparison to patients without AKI (1.9%). Although having an episode of AKI conferred a greater risk of increase in level of care post-discharge there was no association with severity of AKI (Table 4).

Hospital readmission

Having an episode of AKI was also associated with an increase in hospital readmission within 30 days compared with those without AKI (Table 4), although this did not associate with severity of AKI.

Table 1 Summaries of mean age, gender, deprivation and co-morbidity at a patient level, only considering admissions during the recruitment period, and for multiple admissions per patient during the recruitment period selecting the patient's admission with the highest AKI stage

Variable	No AKI (n = 15,478)	AKIN 1 (n = 3,067)	AKIN 2 (n = 807)	AKIN 3 (n = 588)	No AKI info (n = 7,496)
Age - Mean (SD)	62.0 (20.3)	74.2 (16.3)	76.1 (14.7)	72.5 (15.7)	54.2 (21.0)
Age: 18-39	17.1%	5.1%	3.6%	4.4%	29.0%
40-59	23.7%	11.3%	8.9%	16.0%	28.3%
60-79	36.9%	38.2%	37.3%	40.7%	29.5%
80+	22.3%	45.5%	50.2%	39.0%	13.2%
Male Sex - %	45.1%	52.2%	45.0%	49.8%	45.8%
Deprivation - Median (IQR)	17.4 (11.8 27.0)	17.2 (11.8, 25.8)	17.3 (11.8, 25.8)	17.2 (11.9, 26.9)	17.2 (11.7, 26.7)
AIDS - %	0.1%	0.1%	0.1%	0.0%	0.0%
Malignancy - %	6.2%	11.5%	14.0%	16.7%	4.8%
CHF - %	2.6%	10.4%	13.9%	11.6%	1.0%
CPD - %	12.8%	17.0%	16.1%	17.4%	8.5%
Cerebrovascular disease - %	7.3%	13.5%	12.3%	11.2%	3.4%
Dementia - %	3.2%	6.7%	8.2%	7.0%	1.9%
Diabetes - %	10.3%	20.2%	18.7%	23.8%	6.0%
Hemiplegia. - %	1.3%	1.8%	1.4%	1.5%	0.5%
Hypertension - %	27.2%	39.%	39.3%	39.0%	15.5%
MI - %	3.0%	5.0%	6.0%	3.9%	0.7%
Solid tumour - %	2.0%	3.2%	4.8%	4.4%	0.9%
Liver disease - %	0.9%	1.8%	3.0%	6.1%	0.5%
PVD - %	2.1%	5.4%	6.2%	4.6%	1.0%
Peptic ulcer - %	0.6%	1.2%	1.7%	1.9%	0.4%
Renal disease - %	1.7%	11.2%	16.4%	22.3%	1.1%
Rheumatic disease - %	2.3%	3.9%	3.1%	4.1%	1.1%
CKD - no data	0%	0%	0%	0.7%	34.4%
no CKD	84.8%	61.9%	62.1%	68.2%	58.0%
CKD stage 3a	10.0%	19.1%	20.1%	15.0%	5.0%
CKD stage 3b	4.0%	13.1%	12.1%	10.2%	2.0%
CKD stage 4	1.0%	5.3%	5.5%	2.6%	0.5%
CKD stage 5	0.2%	0.5%	0.2%	3.4%	0.1%
Charlson ≤ 0 - %	58.0%	31.9%	25.8%	23.3%	74.5%
1-10 - %	25.9%	29.4%	30.5%	30.1%	17.4%
11 + =%	16.2%	38.8%	43.7%	46.6%	8.2%

Chronic pulmonary disease (CPD), chronic heart failure (CHF), myocardial infarction (MI), peripheral vascular disease (PVD), acquired immunodeficiency syndrome (AIDS).

Discussion

Summary of main findings

The incidence of AKI in an adult population reported here, 15,325 pmp/yr (10,534 pmp/yr with AKIN 1, 2,772 pmp/yr with AKIN 2 and 2,020 pmp/yr with AKIN3), is significantly higher than previous estimates reported in the literature, [20] and is likely to be closer to the real incidence in the population. The reasons for the higher incidence we report here are several. This is an unselected in-hospital population; there is increased testing of creatinine due to heightened awareness; the laboratory service in East Kent comprehensively covers the catchment population; in general because of the geography of our catchment area all patients in the area are admitted to one of our three hospital sites; our population is older in comparison to the United Kingdom average; and finally, use of the the La France methodology will also increase the reported incidence.

Table 2 A summary of the length of stay for: all patients, those who died in hospital, and those who survived to hospital discharge, split by AKI stage

Statistic	No AKI (n = 20,464)	AKIN 1 (n = 3,961)	AKIN 2 (n = 927)	AKIN 3 (n = 633)	No AKI info (n = 10,030)
All patients					
Mean (SD)	4.5 (10.5)	9.7 (14.6)	12.3 (16.0)	14.9 (18.5)	2.3 (9.8)
Median (IQR)	2 (0, 5)	5 (1, 12)	7 (3, 15)	9 (4, 20)	1 (0, 2)
Died in hospital					
Mean (SD)	11.1 (14.4)	11.8 (16.3)	10.0 (11.9)	10.3 (12.2)	13.5 (29.1)
Median (IQR)	6 (2, 14)	6 (2, 15)	6 (2, 14)	6 (2, 14)	5 (1, 15)
Survived to hospital discharge					
Mean (SD)	4.4 (10.4)	9.5 (14.5)	13.0 (17.1)	17.2 (120.5)	2.1 (8.8)
Median (IQR)	1 (0, 5)	5 (1, 11)	8 (3, 15)	11 (5, 22)	1 (0, 2)

Length of stay is summarised as a continuous variable, and then additionally split into categories.

In this current study we have clearly demonstrated that patients with AKI, even after correcting for age, gender, co-morbidity, and CKD, have an increase in morbidity and mortality both in the short and long term in comparison to patients without AKI. These outcomes also hold true for small changes in SCr (AKIN 1). In comparison with patients with no AKI those with AKIN 1 had a 52% longer hospital stay, a 2.8-fold increased risk of admission to ITU, a 39% longer ITU stay (in those who went to ITU), and a 2.4-fold greater in-hospital mortality. Furthermore, patients with AKIN 1 had twice the long term risk of death, a 33% higher likelihood of an increase in care, and a 42% higher risk of re-admission within 30 days. In those patients with AKIN 3 (the subject of the NCEPOD report) [27] hospital LOS doubled, there was a 22 times higher risk of admission to ITU and ITU LOS was also doubled, consistent with national data from the Intensive Care National Audit and Research Centre [28]. Acute RRT support was required in 13.1% of patients with AKIN 3. Hospital mortality was 26-fold greater and in those surviving to leave hospital there was a 5.5-fold increased risk of subsequent death. Patients with AKIN 3 had a 7% higher risk of requiring an increase in care and had a 54% higher risk of re-admission within 30 days than patients with no AKI. Overall, 0.45% of patients with AKI and 3.40% of patients with AKIN 3 subsequently required chronic RRT.

As the time of entry into the cohort was the date of admission for each patient there is the possibility of reverse causality, for example a patient who has a longer length of stay may have a greater risk exposure to the development of AKI. However in this cohort, of the 5521 admissions with AKI, 4064 (73.6%) already had AKI on admission.

Strengths and weaknesses of study

The population-based analysis reported here considers all patients admitted in a general hospital setting in the United Kingdom during a 6 month period. The catchment population for this cohort is from East Kent in the South East Coast of England. Incomparison to the wider population in England East Kent has an older population (mean age 42 years compared to the national mean age of 39) but with fewer ethnic minorities (6.3% of Black and Ethnic minority compared with 14.6% nationally) [21]. Nevertheless, we believe that data linkages between the pathology, hospital data warehouse and renal systems have enabled us to come closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date.

This study is a retrospective database study and clearly has limitations. Key to the definition of AKI is knowledge

Table 3 A summary of the survival estimates at 6-month intervals along with corresponding confidence intervals

Variable	No AKI	AKIN 1	AKIN 2	AKIN 3
6 m survival (95% CI)	0.94 (0.94, 0.94)	0.77 (0.75, 0.78)	0.48 (0.45, 0.52)	0.39 (0.35, 0.43)
12 m survival (95% CI)	0.92 (0.92, 0.93)	0.70 (0.68, 0.71)	0.37 (0.34, 0.40)	0.28 (0.25, 0.31)
18 m survival (95% CI)	0.91 (0.91, 0.92)	0.65 (0.63, 0.66)	0.32 (0.29, 0.35)	0.22 (0.19, 0.25)
24 m survival (95% CI)	0.90 (0.89, 0.90)	0.59 (0.58, 0.61)	0.27 (0.24, 0.29)	0.18 (0.16, 0.20)

Note that the AKI groups are based on 'upgraded' AKI risk. If a patient experiences a subsequent admission during follow-up with a higher stage of AKI, they will be upgraded at that point to the higher group.

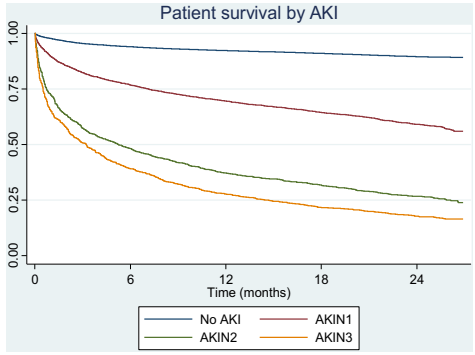

Figure 2 Kaplan-Meier survival by stage of AKI. Note that the AKI groups are based on 'upgraded' AKI risk.

of pre-morbid kidney function (baseline SCr) and the threshold value of SCr from which change is measured (reference SCr). The importance of baseline SCr is in the determination of pre-existing CKD and this value should be based on SCr values available > 3 months prior to the index event. The reference SCr should be ideally be the lowest SCr recorded within 90 days of the event to distinguish this value from the baseline SCr. However, practically in many cases there may be either few or no pre-hospitalisation SCr values making distinction between baseline and reference SCr impossible. This is an area that requires further guidance and consensus from the international community and various strategies have been suggested including varying the baseline/reference creatinine from admission to 365 days prior [22], taking the average of values between 7–365 days prior to admission [29], back calculating reference SCr for missing values from an assumed MDRD glomerular filtration rate of 75 ml/min/1.73 m^2 [30], and (most recently) a method employing multiple imputation using known comorbidity strengthened by factoring in the lowest admission SCr [31]. For simplicity we chose to use the lowest SCr in the 12 months prior to the acute rise to define AKI. It may be that by doing this we have included patients with progressive CKD and defined them as AKIN 1. However, as Lafrance et al. demonstrated and our data confirms, patients with AKIN 1 using this methodology still have a significantly increased likelihood of a specific adverse outcome occurring compared to patients with no AKI [22].

The lowest serum creatinine in the 12 months following discharge was utilised to categorise AKI (for those without pre-hospitalisation creatinine) in 8.2% of admissions with AKI. We acknowledge that the assumption that AKI was present if serum creatinine improved following admission by greater than 26.4 μmol/L may not always be correct but use of this methodology was only necessary in 8% of those categorised as having AKI. The

Table 4 Regression analyses examining the association between severity of AKI and survival, in-hospital mortality, LOS, ITU utilisation, increase in care and readmission

		Risk of death	In-hospital mortality	ITU transfer	Increase in care	Hospital re-admission	Relative length of stay	Relative ITU length of stay
Model	Stage of AKI	Hazard ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Ratio (95% CI)	Ratio (95% CI)
1	No AKI	1	1	1	1	1	1	1
	AKIN 1	4.85 (4.51, 5.21)	4.29 (3.68, 5.01)	2.36 (1.90, 2.93)	2.71 (2.17, 3.38)	1.93 (1.75, 2.13)	1.90 (1.84, 1.97)	1.38 (1.13, 1.68)
	AKIN 2	12.0 (11.0, 13.1)	16.8 (13.5, 21.1)	4.72 (3.36, 6.61)	3.71 (2.56, 5.38)	2.25 (1.83, 2.76)	2.58 (2.43, 2.75)	1.54 (1.17, 2.01)
	AKIN 3	15.6 (14.2, 17.1)	24.7 (18.8, 32.3)	23.8 (16.4, 34.6)	2.27 (1.36, 3.81)	2.09 (1.61, 2.72)	3.07 (2.85, 3.30)	2.25 (1.85, 2.73)
2	No AKI	1	1	1	1	1	1	1
	AKIN 1	3.11 (2.89, 3.35)	2.98 (2.53, 3.52)	2.63 (2.11, 3.28)	1.61 (1.29, 2.01)	1.69 (1.53, 1.87)	1.68 (1.62, 1.74)	1.43 (1.17, 1.74)
	AKIN 2	7.54 (6.89, 8.25)	13.5 (10.5, 17.5)	5.43 (3.88, 7.61)	2.07 (1.43, 2.97)	2.00 (1.63, 2.46)	2.22 (2.09, 2.36)	1.56 (1.20, 2.04)
	AKIN 3	11.6 (10.6, 12.7)	25.2 (18.6, 34.5)	23.9 (16.6, 34.4)	1.56 (0.93, 2.60)	1.94 (1.49, 2.53)	2.72 (2.53, 2.92)	2.27 (1.88, 2.76)
3	No AKI	1	1	1	1	1	1	1
	AKIN 1	1.89 (1.74, 2.04)	2.41 (1.99, 2.91)	2.76 (2.20, 3.46)	1.33 (1.06, 1.67)	1.42 (1.29, 1.57)	1.52 (1.47, 1.58)	1.39 (1.14, 1.69)
	AKIN 2	3.81 (3.46, 4.18)	12.1 (8.84, 16.5)	6.03 (4.58, 8.51)	1.49 (1.02, 2.16)	1.50 (1.23, 1.83)	1.88 (1.77, 2.00)	1.42 (1.07, 1.87)
	AKIN 3	5.49 (4.97, 6.06)	26.3 (17.8, 38.8)	22.4 (15.5, 32.2)	1.07 (0.64, 1.80)	1.54 (1.20, 1.99)	2.16 (2.01, 3.32)	2.18 (1.77, 2.68)

Model 1. Unadjusted. Model 2. Adjusted for age and gender. Model 3. Adjusted for age, gender, primary diagnosis, modified Charlson co-morbidity score, stage of chronic kidney disease (CKD), admission from residential or nursing care, deprivation index, hospital admissions and outpatient appointments in the last 12 months. All values are statistically significant, with p values < 0.001. The outcomes are defined as follows: ITU transfer - a patient being transferred to and spending any time in ITU during their hospital stay; Increase in Care - a patient being admitted from home and being discharged to residential or nursing care; Hospital Re-admission – a patient being re-admitted to hospital within 30 days following discharge; Relative Length of Stay – the ratio of length of stay in comparison to the length of stay of a patient without AKI; Relative ITU Length of Stay – the ratio of ITU length of stay (in those patients who went to ITU) in comparison to the length of stay in ITU of a patient without AKI.

incidence of AKI in admissions utilising a post discharge baseline (9.9%) was less than in those where pre-admission creatinine data was available (16.1%).

We cannot be certain that none of the patients with insufficient SCr data experienced AKI. These patients were significantly younger and had less co-morbidity than those with sufficient SCr data and either had one or no SCr result prior to, or following hospital admission. Survivors (9,830 of 10,030) were also short stay patients (LOS 0–2 days) and were therefore unlikely to have sustained any degree of AKI. The 200 patients in this group who did not survive the hospital admission had a mean LOS of 13.5 days, lack of baseline SCr data precluded derivation of AKI status in these patients. This also raises the issue of possible ascertainment bias, that sicker patients may have more creatinine tests, increasing the probability of detecting AKI.

Co-morbidity data was extracted from the hospital data warehouse using validated algorithms, however this still relies on the accuracy of coding of clinical episodes which may not necessarily be correct. This also applies to the analysis of increase in care on discharge which replies on the accurate coding on the PAS at time of discharge.

While the statistical models used in this analysis have accounted for multiple confounders identified in the literature to date there is always the possibility that there may be other confounders hitherto unknown.

Finally, despite our estimates of the incidence of AKI in a typical general hospital setting being the highest to date, EKHUFT does not provide cardiothoracic, liver or burns services and our reported incidence of AKI may still be an under-estimation of the total population incidence.

Conclusions

This data comes closer to the real incidence and outcomes of AKI managed in-hospital than any study published in the literature to date. Nine percent of all admissions and 15 percent of non-maternity and non-day case admissions to hospital sustained an episode of AKI with increased subsequent short and long term morbidity and mortality, even in those with AKIN1. What this study adds to existing knowledge is data enabling a much more accurate assessment of the overall impact of AKI on the healthcare economy. We provide data concerning hospital and intensive care mortality, LOS, readmission and RRT usage. We also detail the rate of RRT after longer term follow up and the social care impact in terms of increased level of care in those surviving an episode of AKI. These increased adverse outcomes from AKI confer an increased burden and cost to the healthcare economy. The data we have presented will enable this cost to be quantified and will furnish a baseline for quality improvement projects aimed at early identification, improved management, and where possible prevention, of AKI.

It has been suggested that milder forms of AKI defined by creatinine criteria may simply represent a marker of general system pathology and multi organ dysfunction, not specifically related to kidney injury per se. Whether this is true or not, AKI defines a group of patients whose outcomes are poor, both in the short and long term, who are sub-optimally managed, and who should represent a focus for patient safety improvement.

With the international agreement on the definition of AKI and its validation in clinic research, it has become clearer how important the effective management and prevention of AKI is. Agreed definitions have provided a comparable platform for the audit of AKI and its management and outcomes, both in hospital and in the community.

Additional file

Additional file 1: Table S1. Primary diagnoses used in the analysis, by ICD-10 group.

Competing interests

None of the authors of this manuscript have a conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Authors' contributions

MB PS CK all contributed to conception and design, interpretation of data, drafting and revising of the manuscript. TW contributed to conception and design, and extraction of data. All authors have given final approval of the manuscript version to be published.

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Appendix 3: Paper 3: The economic impact of acute kidney injury in England

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Original Article

The economic impact of acute kidney injury in England

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ABSTRACT

Background. Acute kidney injury (AKI) is one of the most common complications affecting hospital inpatients around the world. It is associated with high mortality and adverse long-term outcomes, but there is uncertainty regarding its prevalence and cost. We estimate the prevalence of AKI in hospital inpatients in a universal health-care system, and the immediate and long-term impacts on survival, quality of life and health-care costs.

Methods. We examined prevalence of AKI in inpatients using both routine national data for the National Health Service (NHS) in England, and laboratory data from East Kent Hospitals. We used regression analyses to estimate the impact of AKI on mortality and length of hospital stay, and a Markov model to estimate the impact on quality-adjusted life years and NHS costs.

Results. AKI was recorded in 2.43% of hospital admissions in Hospital Episode Statistics (HES), but age- and gender-standardized estimates derived from laboratory data suggest the true prevalence may be more than five times as high (14.15%). We estimate that the annual number of excess inpatient deaths associated with AKI in England may be above 40 000. The annual cost of AKI-related inpatient care in England is estimated at £1.02 billion, just over 1% of the NHS budget. The lifetime cost of post-discharge care for people who had AKI during hospital admission in 2010–11 is estimated at £179 million.

Conclusions. AKI prevalence in inpatients may be considerably higher than previously thought, and up to four fifths of cases may not be captured in routine hospital data. AKI is associated with large numbers of in-hospital deaths and with high NHS costs. Comparison of HES and East Kent data suggests that most of the cases recorded in HES may be relatively severe AKI (AKIN 2–3).

Keywords: acute kidney injury, cost, economics, mortality

INTRODUCTION

Acute kidney injury (AKI) is one of the most serious and common complications affecting hospital inpatients, and incidence is believed to be rising [1–4]. It is associated with adverse outcomes and high mortality, independent of other risk factors [5–7]. Even mild cases of AKI are associated with increased in-hospital mortality risk [8], and patients who recover kidney function after AKI are at increased risk of developing chronic kidney disease (CKD) and of death [9]. There is evidence that deficiencies in clinical care may contribute to the development and progression of the condition. In the UK, a recent report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) [10] found that 30% of AKI cases occurring during hospital admission were avoidable, and that only 50% of patients with AKI received an overall standard of care that was considered good.

Measurement of the incidence and prevalence of AKI, and analysis of outcomes, have in the past been hampered by the lack of an agreed definition. Most studies have focused on relatively severe AKI [11, 12], on AKI in intensive care units [13–16] or on patients who require renal replacement therapy (RRT) [17, 18]. A 2002 study found that 7.2% of patients at a US centre acquired some degree of renal impairment during hospital admission [19]. Newly developed classification systems in recent years have focused on AKI as a spectrum of disease, and create the potential for more robust measurement of prevalence and outcomes [20–22].

This study examines AKI among inpatients, estimating prevalence, mortality, outcomes and the cost to the National Health Service (NHS) in England. The analysis is based, in the

first instance, on Hospital Episode Statistics (HES), which provide details of patient demographics and health-care activity, including recorded diagnoses, procedures, length of stay and in-hospital mortality for all individual hospital admissions in the English NHS. The national dataset is derived from patient records at each hospital. HES data do not, however, provide details of AKI stage, or of pre-admission or post-discharge kidney function, and it is generally accepted that AKI is under-recorded on patients' notes.

We therefore compare the national findings with data from East Kent Hospitals University NHS Foundation Trust (EKHUFT). At East Kent, laboratory records were used to identify AKI, the condition was classified using the Acute Kidney Injury Network (AKIN) system [21], prior CKD status was ascertained and patients were followed for up to 2 years after discharge.

We use age- and gender-standardized extrapolation from the study findings to provide an indication of the possible level of under-recording of AKI in patient records and routine datasets, of the distribution of AKI by AKIN stage, of prior CKD status and of post-discharge health status and care needs.

MATERIALS AND METHODS

Our analysis used HES data to measure the recorded prevalence of AKI in hospital admissions in England, the age and gender distribution of people with AKI, survival to discharge and the impact of AKI on inpatient costs. These findings were compared with data from EKHUFT, a group of three inpatient hospitals in the South of England, which serves a defined population of ~720 000 people. In both cases, the analysis was restricted to adults (aged ≥ 18). Elective day case and maternity admissions were excluded. In addition, patients on chronic RRT were excluded from EKHUFT data, but could not be discretely identified in HES.

Data

We examined all finished hospital admissions during 2010–11 in HES, and identified those with a recorded diagnosis of AKI, using International Classification of Diseases (ICD-10) codes N17 or N280.

The EKHUFT data covered admissions from 1 February to 31 July 2009 inclusive. Patients with AKI during admission were identified and classified by the AKIN criteria using serum creatinine (SCr) data from pathology records [21]. The pathology records used covered all SCr tests commissioned in primary, community and acute sectors from 1 February 2008 to 31 July 2010. Baseline SCr was estimated using the lowest level recorded in the 12 months prior to hospital admission, after the method of LaFrance *et al.* [23], and this was compared with the highest SCr recorded during hospital admission in the study period. In cases where there were no pre-hospitalization values and the follow-up SCr (lowest in the 12 months following discharge) was lower than the peak in the study admission, the follow-up value was used as the reference SCr. In these cases the assumption was made that, if SCr fell by more than 26.4 μmol/L after discharge, the admission involved an AKI. Cases where no SCr value was available for either the 12 months preceding or the 12 months following admission were recorded as 'AKI status unknown'.

The lowest SCr recorded in the 12 months before admission was also used to estimate baseline glomerular filtration rate (eGFR). Patients with baseline eGFR <60 mL/min were identified as having prior CKD, and eGFR levels were used to classify stages 3–5 CKD [24].

For both HES and EKHUFT data, we calculated AKI prevalence for four patient age bands (18–39, 40–59, 60–79, 80+) sub-divided by gender to produce eight sub-groups. We applied the EKHUFT prevalence figure for each of the sub-groups to the admission numbers recorded in HES, to produce an England-level prevalence estimate standardized for age and gender.

Inpatient analysis

We estimated the impact of AKI on mortality and length of stay in both datasets, using regression analyses. The impact on days in critical care was examined in EKHUFT only. The impact of AKI on mortality (odds ratio) was estimated using multivariate logistic regression. The impacts on length of hospital stay and on days in critical care were estimated using multilevel negative binomial regression. Two-level models were used with individual admissions nested within patients. Covariates used in the HES analysis were AKI diagnosis, patient age, gender, index of multiple deprivation score, admission method (elective or non-elective) and specialty type (surgical or non-surgical). Covariates used in the EKHUFT regressions were age, gender, index of multiple deprivation score, admission method (elective or non-elective), admission source (home or not), admission day (weekend or week day), CKD diagnosis and stage, number of hospital admissions in the previous 12 months, number of outpatient appointments in the previous 12 months, comorbidities and primary diagnosis. A complete list of covariates is provided in the Supplementary Appendix. Analyses were carried out in Stata versions 8 and 12.1.

We report results as means with standard deviations or as ratios with 95% confidence intervals. Further detail on prevalence, mortality, CKD status and AKI status at hospital admission are provided in the Supplementary Appendix.

Inpatient costs

We estimated acute costs related to AKI for general inpatient care and critical care. For general inpatient care, separate cost estimates were derived from HES and EKHUFT activity data. Cost estimates for critical care were based on EKHUFT data only, as HES do not provide robust data in this area.

Most inpatient care in the English NHS is reimbursed through national tariffs, which are set at Healthcare Resource Group (HRG)-level. HRGs are groups of health-care activities that are clinically related and similar in cost. Each admission is grouped to a single HRG, using ICD-10 and OPCS Classification of Interventions and Procedures (OPCS-4) codes. In admissions with multiple diagnoses and/or procedures, the HRG relating to the most expensive health-care activity is generally selected.

For admissions grouped to AKI-specific HRGs, we attributed the entire cost of the admission to AKI, and used the tariff price to estimate unit cost [25]. Tariff prices vary around England, depending on local cost differences. A formula known as the Market Forces Factor (MFF) is used to make these local adjustments. Prices used here are estimated using the average MFF for the country.

However, most admissions with recorded AKI are grouped to non-AKI HRGs, reflecting the fact that AKI frequently occurs in patients who have multiple interventions and/or diagnoses. For admissions in which the patient had AKI, but the admission was grouped to a non-AKI HRG, the cost impact of AKI was estimated using regression analyses on length of stay. Costs were estimated for excess bed days associated with AKI, using the mean cost of a hospital bed day for AKI HRGs (LA07C-G) in NHS Reference Costs for acute hospitals (£311) as an estimate of unit cost [26].

The cost of excess critical care days associated with AKI was estimated, based on the critical care regression analysis outlined above. The average unit cost of a critical care bed day was estimated from NHS Reference Costs (£1213) [26].

Long-term impacts and costs

We constructed a Markov model to estimate long-term quality-of-life impacts and costs arising from excess CKD and RRT in patients who have had AKI, relative to a matched group without AKI. The model was run for a representative patient aged 72 at outset (estimated from age distributions in HES and EKHUFT). Parameters were estimated based on data from EKHUFT, UK Renal Registry, Office for National Statistics, NHS Blood and Transplant and earlier studies (Table 1). Supplementary regression analysis on mortality (Poisson with scaled standard errors to correct for over-dispersion) was conducted to estimate relative risk for use in the Markov model. Quality-adjusted life years (QALYs) were estimated using EQ-5D utilities derived from a recent meta-analysis [27]. Model structure is shown in Figure 1. Analysis was carried out in TreeAge Pro.

Sensitivity analysis

In sensitivity analysis, we applied the upper and lower bound 95% confidence interval estimates for AKI prevalence in each of the age and gender sub-groups at EKHUFT to HES

Table 1. Markov model parameters and sources

Parameters		Estimated value	Source
% of patients with CKD Stage 3 at hospital admission	AKI and comparator	34.18%	East Kent data–AKI group. Same prevalence is applied in model to comparator.
% of patients who die during hospital admission	AKI	17.44%	East Kent data
	Comparator	4.98%	East Kent data: % of patients with AKI who die/relative risk of death in AKI
% of patients on RRT 90 days after discharge	AKI	0.26% in base case, 0.11% and 0.42% in sensitivity analysis	East Kent data (excluding patients with CKD Stage 4 or 5)
	Comparator	0.00%	East Kent data
Annual transition probabilities			
Normal kidney function to CKD	AKI	2.50%	Bucaloiu *et al.* (2012) [9] Baseline risk of de novo CKD × HR with reversible AKI event
	Comparator	1.31%	Bucaloiu *et al.* (2012) [9]
CKD to RRT	AKI and comparator	0.17%	Incidence of RRT England (Renal Registry 2011) [28] minus estimated RRT 90 days after AKI (East Kent)/CKD prevalence England (HSE 2010) [29]
Dialysis to transplant	AKI and comparator	7.05%	(Transplant incidence 2010–11, England (NHSBT), [30] minus transplant within 90 days of starting RRT (Renal Registry 2011)) [28]/Prevalent dialysis England (Renal Registry 2011) [28]
Transplant graft failure	AKI and comparator	2.50%	Renal Registry 2011 [28]
Normal kidney function to death	AKI and comparator		ONS Life Tables by year of age, [31] adjusted for CKD and RRT mortality. CKD prevalence by age band from Health Survey for England 2010, [29] CKD mortality from Matsushita *et al.* (2010), [32] RRT prevalence by age Renal Registry 2011, [28] RRT mortality rate by age band Renal Registry 2011 [28]
CKD to death	AKI and comparator	RR = 1.28	Normal kidney function risk by age × RR of death by CKD stage from Matsushita *et al.* (2010) [32], Distribution of CKD by stage from de Lusignan *et al.* (2011) [33]
RRT to death	AKI and comparator		Mortality rate in RRT by age band from Renal Registry report, 2011 [28]
Annual cost			
CKD Stages 3–4		£241	Kerr *et al.* (2012) [34] updated to 2010–11 prices
Dialysis		£27 765	
Transplant year 1 (including pre-transplant care)		£34 036	
Transplant after year 1		£7520	
EQ-5D			
Normal kidney function		0.78	UK population norm, age 65–74 from Kind *et al.* (1999) [35]
CKD Stages 3–4		0.72	Wyld *et al.* [27]
Dialysis		0.63	
Transplant		0.75	

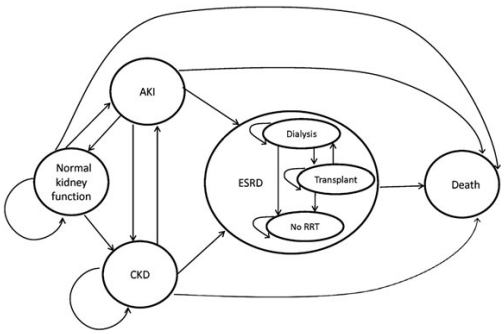

FIGURE 1: Structure of Markov model.

admission figures. We summed the lower and upper bound estimates, respectively, and used the resulting prevalence estimates to derive cost and QALY estimates.

We also re-ran the Markov model using the 95% confidence interval bounds for the proportion of patients requiring RRT at 90 days post-discharge from the EKHUFT data.

RESULTS

Prevalence

HES data record 5 881 635 inpatient admissions for 3 792 951 patients in 2010–11. AKI was recorded in 142 705 of these admissions (2.43%) and 122 928 patients (3.24%) had at least one admission with recorded AKI during the year. Prevalence ranged from 0.32% in patients aged 18–39 to 5.74% in those aged ≥80 (Figure 2).

During the 6-month study period at EKHUFT, there were 36 015 admissions (27 436 patients). Laboratory data indicate that AKI was present in 5521 admissions and that 4462 patients had at least one admission with AKI, a prevalence of 15.33% of admissions and 16.26% of patients. The EKHUFT inpatient population is older than that in HES (Figure 3). The age- and gender-standardized prevalence for England is estimated at 14.15% of admissions and 14.65% of patients.

At EKHUFT, 38.10% of patients who had AKI during the study period had pre-existing CKD stage 3–5. In 73.37% of admissions with AKI, the patient had AKI when admitted to hospital. Further detail is provided in the Supplementary Appendix.

Mortality

In 40 109 (28.11%) admissions with recorded AKI in HES, the patient died before discharge. Mortality rates increased with age. The odds ratio for death in hospital for patients with AKI relative to those without AKI was 10.52 (95% confidence interval 9.93–11.16). The relative risk of death in hospital for patients with AKI was 4.69 (4.59–4.80) (Table 2).

In 13.93% of admissions with AKI at EKHUFT, the patient died before discharge. Of all inpatient deaths, 55.77% occurred in patients with AKI. The odds ratio and relative risk for in-hospital mortality at EKHUFT increased by AKIN stage (Table 3).

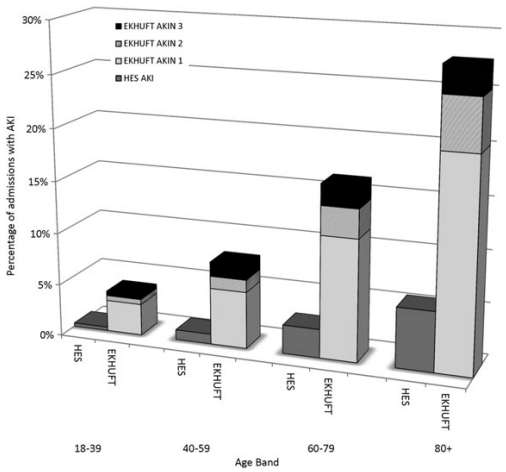

FIGURE 2: Percentage of admissions with AKI, HES and EKHUFT.

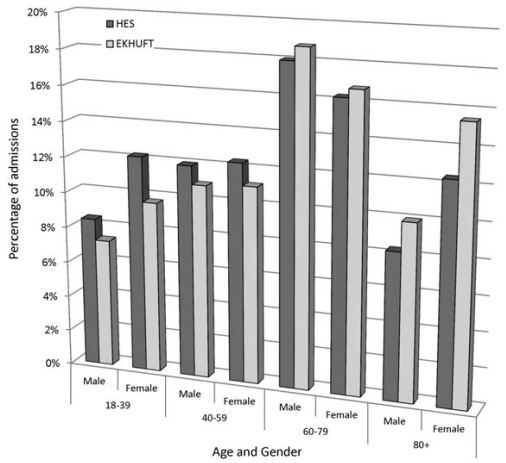

FIGURE 3: Age and gender distribution of admissions, HES and EKHUFT.

Table 2. Length of stay and mortality, by AKI status, HES data

	No AKI	AKI	P value
Length of stay			
Mean (SD)	5.14 (11.56)	16.47 (19.71)	
Ratio (95% CI)	1	2.57 (2.54, 2.60)	<0.001
In-hospital mortality			
% Mortality	1.99%	28.11%	
Odds ratio (95% CI)	1	10.52 (9.93, 11.16)	<0.001
Relative risk (95% CI)	1	4.69 (4.59, 4.80)	<0.001

Table 3. Length of stay, critical care days and in-hospital mortality in admissions, by AKI status, EKHUFT

	No AKI	All AKI	AKIN 1	AKIN 2	AKIN 3	AKI status unknown	P value
Length of stay							
Mean (SD)	4.5 (10.5)	10.72 (15.44)	9.7 (14.6)	12.3 (16.0)	14.9 (18.5)	2.3 (9.8)	
Ratio (95% CI)	1	1.62 (1.57, 1.68)	1.52 (1.46, 1.58)	1.88 (1.77, 2.00)	2.16 (2.00, 3.32)	0.45 (0.43, 0.47)	<0.001
Critical care							
Mean (SD)	0.05 (1.02)	0.35 (2.35)	0.17 (1.74)	0.31 (1.80)	1.57 (4.78)	0.02 (0.51)	
Ratio (95% CI)	1	4.32 (3.63, 5.14)	2.60 (2.10, 3.21)	5.61 (4.15, 7.58)	18.2 (14.4, 23.1)	0.02 (0.01, 0.05)	<0.001
In-hospital mortality							
% Mortality	2.00%	13.93%	8.10%	25.60%	33.30%	1.97%	
Odds ratio (95% CI)	1	5.11 (4.23, 6.17)	2.51 (2.06, 3.05)	13.3 (9.67, 18.3)	30.8 (20.7, 46.0)	1.49 (1.12, 1.99)	<0.001
Relative risk (95% CI)	1	3.50 (3.30, 3.70)	2.11 (1.98, 2.26)	5.79 (5.38, 6.22)	8.94 (8.28, 9.64)	1.31 (1.18, 1.44)	<0.001

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Length of stay

Mean length of stay in HES was 16.47 (SD 19.71) days for admissions with AKI, and 5.14 (SD 11.56) days for admissions without recorded AKI. Multivariate regression analysis indicated that AKI diagnosis was associated with a length of stay 2.57 (95% CI 2.54–2.60) times as high as that for admissions without AKI (Table 2).

At EKHUFT, AKI was associated with hospital stays 1.62 (1.57–1.68) times as long as those for patients without AKI. The impact on length of stay associated with AKI increased with AKIN stage (Table 3).

Critical care

At EKHUFT, 59.89% of critical care bed days were for people with AKI. In multivariate regression analysis, AKI was associated with critical care bed day usage 4.32 (3.63–5.14) times the level of patients without AKI (Table 3).

Long-term outcomes

HES data do not provide details of post-discharge outcomes. Data from EKHUFT indicate that, 90 days after discharge, 0.56% of patients with AKI were on RRT. However, more than half this group had pre-existing CKD Stages 4–5, so it is possible that their progression to RRT might have occurred without AKI and, indeed, that their AKI may have been due to rapidly progressing CKD. Of patients with AKI and CKD Stages 1–3, or no CKD, 0.26% were on RRT 90 days after discharge. If this pattern were repeated at national level, and if the prevalence of CKD, by stage, in inpatients with AKI were the same as at East Kent, it is estimated that 1369 (95% CI 561–2178) people a year who had AKI during an inpatient admission, and who did not have pre-existing CKD Stage 4 or 5, would require RRT 90 days after discharge.

Costs

In HES, 23 145 admissions in 2010–11 were grouped for payment to HRGs specific to AKI (LA07A-C), 16.22% of all admissions with a recorded AKI diagnosis. The total tariff cost of these LA07 admissions was £75 million (Table 4).

Based on the HES regression analysis findings, it is estimated that, in 2010–11, there were 977 116 excess bed days associated with AKI in 119 560 admissions grouped to HRGs other than LA07. The cost of these excess bed days is estimated at £304 million.

Table 4. Activity and expenditure, admissions grouped to Healthcare Resource Groups for Acute Renal Failure, HES 2010–11

HRG	Elective		Non-elective	
	Activity	Cost	Activity	Cost
LA07A				
Acute renal failure with major CC[a]	165	£636 524	10 216	£42 082 937
LA07B				
Acute renal failure with intermediate CC[a]	228	£359 100	11 581	£30 446 234
LA07C				
Acute renal failure without CC[a]	45	£33 752	910	£1 627 841
Total	438	£1 029 376	22 707	£74 157 012

[a]CC, complications or comorbidities.

If the prevalence of AKI identified in laboratory data at East Kent is representative, the number of annual admissions with AKI in England is estimated at 832 235. Based on the EKHUFT regression analysis, the number of excess bed days associated with AKI in admissions grouped to HRGs other than LA07 in England is estimated at 2 565 514. Of these, 163 423 days are estimated to have been in critical care units.

Total inpatient expenditure associated with AKI admissions recorded in HES (excluding critical care use) is estimated at £380 million. Extrapolations from EKHUFT produce an estimate of £1.02 billion for inpatient expenditure related to AKI in England (Table 5).

The Markov model estimates the lifetime cost of post-discharge care for people who have had AKI as inpatients in 2010–11 at £179 million. These costs arise through higher incidence of CKD and RRT, relative to a matched population without AKI. The lifetime QALY loss is estimated at 1.4 per inpatient with AKI.

Sensitivity analysis

Using the lower bounds of the 95% confidence interval for each sub-group at EKHUFT, and standardizing for the age and gender of the HES population, we estimate the number of admissions with AKI in England at 740 964 (494 288 patients) in 2010–11. Using the upper bounds, we estimate

Table 5. Estimated expenditure related to AKI, England 2010–11, based on HES data and extrapolations from EKHUFT

	HES	Extrapolation from EKHUFT
Admissions to LA07 HRGs[a]	£75 186 389	£75 186 389
Excess length of stay in other HRGs	£304 364 710	£750 463 603
Critical care	No data available	£198 232 502
Total inpatient care	£379 551 099	£1 023 882 494
Post-discharge care	No data available	£179 345 543
Total care	£379 551 099	£1 203 228 037

[a]LA07: Healthcare Resource Groups (HRGs) for Acute Renal Failure.

Table 6. Estimated expenditure related to AKI, England 2010–11, sensitivity analyses, based on extrapolations from EKHUFT

	Lower estimate	Upper estimate
Sensitivity analysis 1		
Excess length of stay in non-LA07 HRGs[a]	£653 360 453	£847 728 441
Critical care	£165 647 101	£230 817 902
Total inpatient care[b]	£894 193 943	£1 153 732 733
Post-discharge care	£159 531 140	£204 601 432
Sensitivity analysis 2		
Post-discharge care	£116 552 207	£246 325 103

[a]LA07: Healthcare Resource Groups (HRGs) for Acute Renal Failure.
[b]Including expenditure on admissions to LA07 HRGs.

admissions at 923 505 and patients at 633 932. In sensitivity analysis 1, we estimated costs based on these prevalence estimates (Table 6).

Another key area of uncertainty is the proportion of patients who require RRT 90 days after discharge. In sensitivity analysis 2, the Markov model was re-run using the upper and lower confidence intervals for post-discharge RRT in patients who have had AKI, from EKHUFT data. Using these values, the lifetime cost of post-discharge care for people who have had AKI during hospital admission is 2010–11 in England is estimated at £117–£246 million (Table 6).

DISCUSSION

The data presented here provide the most comprehensive estimate to date of AKI prevalence in inpatients in England. The figure based on laboratory data and AKIN classification is considerably higher than earlier estimates based on sub-sets of the AKI population. The comparison with HES data suggests that there may be substantial under-recording and possibly under-recognition of AKI in English hospitals.

Our study finds that AKI is associated with high mortality; the relative-risk estimates from the HES regression analysis suggest that AKI was associated with ~15 000 excess deaths among inpatients in England in 2010–11, while extrapolations from EKHUFT data suggest the annual number of excess deaths associated with AKI in England may be above 40 000. We also find that AKI is associated with large QALY losses.

The EKHUFT data suggest that mortality and length of hospital stay increase with AKIN stage. Mortality in admissions with recorded AKI in HES was higher than that for AKIN 1 and AKIN 2 at EKHUFT, and lower than that for AKIN 3. The mean length of stay for admissions with recorded AKI in HES was higher than that for all AKIN stages at EKHUFT. While there are multiple factors that impact on mortality and length of stay, these findings may suggest that relatively severe AKI (AKIN 2 or 3) is more frequently recorded in HES than AKIN 1. More than 70% of AKI cases at East Kent were AKIN 1.

The financial burden of AKI, as estimated here, is substantial, equivalent to just over 1% of the NHS budget for England in 2010–11.

The EKHUFT population is older and less ethnically diverse than that of England. While the extrapolated prevalence estimates presented here have been standardized for age and gender, it was not possible to adjust for ethnicity. Further study is needed to examine AKI prevalence in an ethnically diverse population in England.

It is also important to note differences between the two datasets and analyses. Patients on RRT were excluded from the East Kent dataset but not from HES. The East Kent regression analyses used a wider range of covariates than those available in HES.

There is uncertainty regarding the incidence of long-term RRT after AKI. The sample size for 90-day post-discharge RRT at EKHUFT was small, and the confidence intervals around the point estimate are correspondingly large. Further studies are needed to examine the impact of AKI on long-term RRT need.

This study focuses only on AKI in adult hospital inpatients. Further research is needed on the incidence and impact of AKI in primary and community care settings.

The recent NCEPOD report in the UK found that 20% of fatal post-admission AKI cases were both predictable and avoidable. Many of the failings identified in that report related to basic medical care, such as checking of electrolytes, performance of physiological observations and adequate senior review. However, at EKHUFT, AKI was present at the point of admission in nearly three quarters of admissions in which AKI occurred. It is likely therefore that efforts to prevent AKI will need to focus on primary and community care as well as on inpatient care.

If 20% of AKI cases were prevented, the figures presented in this report suggest that the gross savings to the NHS could be in the region of £200 million a year, equivalent to 0.2% of the NHS budget in England. It is hoped that the estimates presented here will provide a foundation for future economic evaluation of prevention and early management interventions for AKI, and of strategies for the prevention of complications in AKI survivors.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest. The contents of this paper have not been published previously in whole or part, except in abstract format.

(See related article by Lewington and Hall. The cost of ignoring acute kidney injury. *Nephrol Dial Transplant* 2014; 29: 1270–1272.)

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Appendix 4: Paper 4: Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care?

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ORIGINAL RESEARCH ARTICLE Open Access

Acute kidney injury: an acceptable risk of treatment with renin-angiotensin system blockade in primary care?

Michael Bedford*, Christopher KT Farmer, Jean Irving and Paul E Stevens

Abstract

Background: Use of renin-angiotensin system (RAS) blockade has become increasingly widespread driven by evidence-based guidance. There is concern about the role of these agents in the genesis of avoidable acute kidney injury (AKI).

Objectives: To investigate the association between AKI and use of RAS blockade.

Design: Multilevel hierarchical analysis of a large cohort of patients registered with UK general practitioners.

Setting: Primary care practices in East and West Kent, United Kingdom.

Patients: 244,715 patients from 27 practices.

Measurements: Demographic, clinical, biochemical and prescription data.

Methods: Analyses of data acquired between 02/3/2004 and 17/04/2012 using multilevel logistic regression to determine the relationship between AKI and use of RAS blockade; further analysed by indication for treatment with RAS blockade.

Results: Sufficient serum creatinine data were available to define AKI in 63,735 patients with 208,275 blood test instances. In 95,569 instances the patient was prescribed a RAS antagonist of which 5.4% fulfilled criteria for AKI. The unadjusted odds ratio (OR) for AKI in those prescribed RAS blockade was 1.93 (1.81-2.06, 95%CI) falling to 1.11 (1.02-1.20, 95%CI) when adjusted for age, gender, co-morbidity, GFR category, proteinuria, systolic blood pressure and diuretic therapy. In patients with an evidence-based indication there was no difference in absolute risk of AKI. However, prescription of RAS blockade in the absence of indication appeared to be associated with greater risk of AKI.
When analysis was repeated with AKIN2/AKIN3 as the outcome, although risk of AKI remained significant when unadjusted (OR 1.73, 95%CI 1.42-2.11, p<0.001), after full adjustment there was no increased risk (OR 0.83, 95%CI 0.63-1.09) in those taking RAS antagonists. However, when analysed by indication AKIN2/AKIN3 was significantly more likely in those prescribed RAS antagonists without indication (OR 2.04, 95%CI 1.41-2.94, p<0.001).

Limitations: Observational database study. No information concerning hospitalisation. Prescribing assumptions and potential inaccurate coding. Potential survival bias; patients surviving longer will contribute more data.

Conclusions: Use of RAS antagonists increased the risk of AKI, independent of common confounding variables. After correction for confounders the risk fell away and became non-significant for moderate and severe AKI. However, where there was no evidence-based indication for RAS antagonists the risk of AKI, whether mild, moderate or severe, remained greater.

Keywords: Acute kidney injury, Renin-angiotensin system blockade, System for Early Identification of Kidney Disease (SEIK)

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Abrégé

Contexte: Vu l'abondance de données probantes en la matière, le recours aux inhibiteurs du système rénine-angiotensine-aldostérone (SRAA) est de plus en plus répandu. Il existe certaines préoccupations quant au rôle de ces agents dans la genèse de l'insuffisance rénale aiguë (IRA) évitable.

Objectif de l'étude: Examiner, au sein d'une cohorte en soins de santé primaires, la présence de liens entre l'IRA et l'utilisation d'inhibiteurs du SRAA.

Type d'étude: Une analyse hiérarchique multiniveaux d'une vaste cohorte de patients suivis par des médecins généralistes du Royaume-Uni.

Contexte: Cliniques de soins de santé primaires situées dans l'est et l'ouest du comté du Kent, au Royaume-Uni.

Patients: Les données ont été recueillies auprès d'une cohorte de 244 715 patients en soins primaires, provenant de 27 cliniques de soins primaires dans l'est et l'ouest du comté du Kent.

Mesures: Données démographiques, cliniques, biochimiques et issues d'ordonnances.

Méthodes: L'analyse des données recueillies entre le 2004/03/02 et le 2012/04/17 a été effectuée par régression logistique multiniveaux afin de déterminer la relation entre l'IRA et l'utilisation d'inhibiteurs du SRAA, et ensuite par indication de traitement avec des inhibiteurs du SRAA.

Résultats: Une quantité suffisante de données relatives à la créatininémie était disponible pour évaluer l'IRA chez 63 735 patients, qui avaient eu au total 208 275 prélèvements sanguins. Chez 95 569 sujets, un inhibiteur du SRAA a été prescrit, et 5,4% (5 194) de ces derniers ont eu un épisode d'IRA. Chez les patientsrecevant un traitement fondé sur des indications probantes, 5,8% (4473 sur 76 517) ont eu un épisode d'IRA. Le risque relatif non ajusté (RR) d'IRA associé à l'utilisation d'un inhibiteur du SRAA était de 1,93 (1,81-2,06, 95% IC), diminuant à 1,11 (1,02-1,20, 95% IC) lorsqu'ajusté pour l' âge, le sexe, la comorbidité, la catégorie de débit de filtration glomérulaire, la protéinurie, la pression artérielle systolique et le traitement diurétique. Chez les patients recevant un traitement par inhibiteurs du SRAA fondé sur des indications probantes, il n'y avait aucune différence de risque absolu d'IRA. Par contre, il semblait y avoir un lien entre la prescription d'inhibiteurs du SRAA en l'absence d'indications probantes et un risque accru d'IRA. Lorsque l'analyse a été répétée avec l'AKIN2/AKIN3 comme critère de jugement, le risque d'IRA associé à l'utilisation d'un inhibiteur du SRAA restait significatif dans le modèle non ajusté (RR 1,73, 95% IC 1,42-2,11, $p < 0,001$), mais aucune augmentation de risque n'a été observée après ajustement (RR 0,83, 95% IC 0,63-1,09). Par contre, le risque d'AKIN2/AKIN3 lié à l'utilisation d'un inhibiteur du SRAA était significativement plus élevée chez les patients qui recevaient ces agents sans indications probantes (RR 2,04, 95% IC, 1,41-2,94, $p < 0,001$).

Limites de l'étude: Étude par observation de données prises dans des cliniques de soins primaires. Aucune information d'hospitalisation disponible (base de données de soins primaires). Interprétation des prescriptions et possibilité de codes erronés. Biais de temps d'immortalité possible : les patients qui vivent plus longtemps contribuent davantage à l'analyse par les prélèvements sanguins.

Conclusions: Notre analyse montre que l'utilisation d'inhibiteurs du SRAA augmente le risque d'IRA. Le risque est indépendant de diverses variables de confusion, dont l'âge, la mesure de base de la fonction rénale, la présence de comorbidité pertinente et la pression artérielle systolique. Après correction pour les variables confusionnelles, le risque diminuait toujours : il devenait non significatif pour l'IRA modérée et sévère. Par contre, le risque d'IRA légère, modérée ou sévère demeurait élevé lorsque l'utilisation d'inhibiteurs du SRAA ne s'appuyait sur aucune indication probante.

Renin angiotensin system blockade is known to be associated with acute kidney injury. This is the first study to examine this association by evidence-based indication. Although renin angiotensin system blockade increases the risk of acute kidney injury overall, in those with an evidence-based indication the majority of the effect is explained by underlying co-morbidity. In people with no evidence-based indication prescription of renin angiotensin blockade is an independent predictor of acute kidney injury.

Background

The use of renin-angiotensin system (RAS) blockade in the form of angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and more recently direct renin inhibitors (DRIs) is now widespread. These agents are effective in lowering of blood pressure, reducing proteinuria and amelioration of chronic kidney disease (CKD) progression [1-3]. Evidence supporting beneficial effects in proteinuric diabetic and non-diabetic kidney disease has informed clinical practice guideline recommendations in both CKD and diabetes [4-6]. Evidence for their benefit in ischaemic heart disease and heart failure has also informed guideline recommendations in the general population [7-10] such that treatment with RAS antagonists has clearly defined high quality evidence-based indications (well-designed, well-executed randomised controlled trials (RCTs) or well-conducted meta-analyses of such studies) in the following patient population settings:

1. proteinuria (albumin:creatinine ratio [ACR] >70 mg/mmol)
2. hypertension and proteinuria (ACR > 30 mg/mmol)
3. diabetes and proteinuria (ACR > 3 mg/mmol)
4. chronic heart failure
5. post acute myocardial infarction

In addition hypertension guidance recommends use of RAS antagonists in those with hypertension and age <55 years or resistant hypertension at any age [8] and in those aged ≥18 years of age with hypertension and CKD [10] (RCTs with minor limitations, well-designed, well-executed non–randomised controlled studies and well-designed, well-executed observational studies or well-conducted meta-analyses of such studies).

Outside these indications there is no evidence to support the choice of RAS antagonists over other classes of anti-hypertensive agent in the management of hypertension, with or without CKD. The majority of patients with CKD will not progress to ESRD and these patients are predominantly managed by primary care in the community. In England during 2012 prescriptions for ACEIs, ARBs and DRIs accounted for 6.0 percent of all prescription items [11]. Not all of these prescriptions will be for evidence-based indications and this widespread use of RAS antagonists has raised questions about possible harm without additional benefit, particularly in the elderly [12].

Despite these concerns over the safety of RAS antagonism, in particular in relation to AKI we do not know the level of risk of AKI associated with the routine prescription of these agents in primary care.

The aim of this study was to examine the relationship between prescription of RAS antagonists and development of AKI in the community.

Methods

We performed a multilevel hierarchical analysis of a large cohort of patients registered with UK general practitioners.

Data were extracted from the System for Early Identification of Kidney Disease (SEIK) database. SEIK is a computerized decision support system developed to assist in the management of CKD. The system extracts anonymised demographic, clinical, biochemical and prescription data from primary care systems. Reports aiding and advising on the management of CKD generated using an automated decision tree matrix and several computer algorithms based on NICE guidance [4-6,8] are then returned to participating practices. For this study data were drawn from 27 GP practices across East and West Kent in the UK. Patients with GFR < 15 ml/min/1.73 m^2 or on renal replacement therapy were excluded.

In initial analyses it was evident that a large proportion of patients may switch between treatment with and without RAS antagonists over time, and therefore comparing outcomes in terms of episodes of AKI between these as 2 distinct groups was not viable. We therefore chose to analyse the data at the serum creatinine blood test level. For each patient we extracted all recorded serum creatinine estimations between 02/3/2004 and 17/04/2012. Each serum creatinine then became a data point "blood test instance" at which we extracted and defined the independent and outcome variables.

In performing the analysis at the blood test level there was then the inherent risk that several blood tests for an individual patient could represent the same episode of AKI. Therefore for a given episode of AKI the analysis algorithm excluded all blood results 30 days either side of the peak AKI result, unless a result within the 30 days no longer defined AKI. In this instance subsequent results were not thought to be part of that AKI episode, either prior to the AKI in the 30 days preceding the peak AKI result or demonstrating recovery in the 30 days post the peak AKI.

At each data point, "blood test instance", we extracted or determined: age, gender, co-morbidity (including hypertension, diabetes, ischaemic heart disease, and heart failure), GFR category, proteinuria, blood pressure readings and prescription data including all anti-hypertensive agents and RAS antagonists. For the purposes of determining proteinuria indications for RAAS antagonists the highest proteinuria result for each patient was used. Proteinuria was categorised as per the KDIGO CKD Clinical Practice Guideline 2012 into three categories: "normal to mildly elevated", ACR (or equivalent) <3 mg/mmol; "moderately elevated", ACR (or equivalent) 3–30 mg/mmol; and "severely elevated", ACR (or equivalent) >30 mg/mmol [13]. There is variance in prescription of anti-hypertensives including

RAS antagonists across primary care in terms of the length of prescription given to patients, and also in the coding of these prescriptions. In some practices the dose prescribed and the number of tablets prescribed is coded, however in others only the tablet strength is coded. We therefore made the assumption that if the last prescription date was within 70 days of the "blood test instance", then the patient was still receiving the medication at that time, this was on the basis that the majority of patients receive a 2 month (60 day) supply of medication. At each "blood test instance" we also defined whether or not a patient had an evidence-based indication for treatment with RAS antagonists as described in the introduction.

In this study the outcome variable of interest was AKI in primary care. AKI was defined by the acute kidney injury network (AKIN) creatinine criteria [14] but using the lowest SCr in the 12 months prior to the date of the peak AKI result as the reference after the method of Lafrance et al [15]. Finally we analysed the association between ACE/ARB and AKIN2/3.

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Statistical methods

The primary aim of this analysis was to examine the association between patients taking RAS antagonists and experiencing episodes of AKI. In the analyses AKI was considered primarily as a binary variable, present or absent (ie AKI or no AKI and AKIN2/AKIN3 or no AKI/AKIN1). A feature of the data was that there were multiple measurements from some patients and as a result of this it was unlikely that the outcome values were all independent of each other. It was likely that outcomes for the same patient at different time periods were more similar than from different patients. Therefore it was necessary to account for this in the data analysis. Due to the binary nature of the outcome, and the lack of independence of the data, the analyses were performed using multilevel logistic regression. Two-level multilevel models were used with individual measurements nested within patients.

The relationship between RAS antagonists and AKI could potentially be confounded by various other parameters. Therefore, the relationships between the two key variables were adjusted for several pre-determined factors. Variables considered as potentially confounding were: age, sex, hypertension, diabetes, ischaemic heart disease (IHD), heart failure, GFR, proteinuria, systolic blood pressure and diuretic usage. The status of each of these was updated at the time of every blood test.

GFR category was used in preference to the baseline GFR value, as there were several particularly large GFR values, which might have been influential in the analyses. The GFR categories used followed the KDIGO CKD Clinical Practice Guideline 2012 classification of CKD [13]. A series of four models were examined, each considering the effects of RAS antagonists with different combinations of adjustments for other variables. Model 1 was unadjusted, model 2 adjusted for age and sex, model 3 for all variables apart from proteinuria and model 4 for all variables.

The first analysis assumed a constant effect of RAS antagonists for all patients. Subsequently all patients remained in the analysis, but the interaction between RAS antagonists and an evidence-based indication for their use was included in the analysis. This allowed the effects of RAS antagonists to vary for patients with and without an indication.

Results

There were 345,986 "blood test instances" from 121,933 patients in a practice population of 244,715. In 137,276 (39.7%) of the "blood test instances" no prior creatinine data were available and the presence or absence of AKI could not be assessed. The baseline characteristics of these subjects showed them to be significantly younger, with very little co-morbidity compared to those with baseline GFR data (Table 1). Only 5 percent had CKD and 21 percent hypertension, unsurprisingly they were prescribed significantly fewer medications and only 13 percent had an evidence-based indication for RAS blockade. 435 "blood test instances" from 83 patients were removed as the patient's baseline GFR was <15 ml/min/1.73 m^2. This left outcome data for 208,275 "blood test instances" from 63,722 patients. Table 1 demonstrates the population demographics of these 63,722 patients at baseline. In 112,706 of these instances the patient was not taking a RAS antagonist, 3.1% (3,440) of these instances fulfilled criteria for AKI. In 95,569 blood test instances the patient was taking a RAS antagonist, 5.4% (5,194) of these instances fulfilled criteria for AKI (Figure 1). Of the 63,722 patients: 27,970 (44%) also had proteinuria testing. Of these 22,552 (35%) had "normal to mildly elevated", 4,473 (7%) had "Moderately elevated" and 945 (1.5%) had "Severely elevated" levels of proteinuria.

The majority of AKI was AKIN stage 1. Of the 3,440 instances where the patient was not taking a RAS antagonist, 3,194 had AKIN 1, 193 had AKIN 2, and 53 had AKIN 3. Of the 5,194 instances where the patient was taking a RAS antagonist, 4,881 had AKIN 1, 246 had AKIN 2, and 67 had AKIN 3.

To examine the possibility that a rise in serum creatinine associated with implementation of RAS antagonism led to a false assumption of AKI we also looked at the number of instances where a blood test occurred within

Table 1 Population and baseline characteristics

	Analysed patients			No baseline GFR within the preceding year
Variable	**Total population**	**No AKI in follow-up**	**AKI in follow-up**	
Population				
Population in the analysis (%)	63,722 (100)	58,904 (92.44)	4,818 (7.56)	49,695
Average age (years)	62.67	61.79	73.42	48.93
Males (%)	28,583 (44.86)	26,097 (44.30)	2,486 (51.60)	21,118 (42.50)
Females (%)	35,139 (55.14)	32,807 (55.70)	2,332 (48.40)	28,577 (57.50)
GFR >60 ml/min/1.73 m^2 (%)	50,283 (78.91)	48,135 (81.72)	2,148 (44.58)	47,175 (94.93)
CKD Stage 3a (%)	9,702 (15.23)	8,402 (14.26)	1,300 (26.98)	2,060 (4.15)
CKD Stage 3b (%)	3,019 (4.74)	2,038 (3.46)	981 (20.36)	399 (0.80)
CKD Stage 4 (%)	718 (1.13)	329 (0.56)	389 (8.07)	61 (0.13)
CKD Total (%)	13,439 (21.09)	10,769 (18.28)	2,670 (55.42)	2520 (5.07)
Hypertension (%)	38,912 (61.07)	34,962 (59.35)	3,950 (81.98)	10,454 (21.03)
Diabetes (%)	10,135 (15.91)	8,815 (14.97)	1,320 (27.40)	904 (1.81)
Ischaemic Heart Disease (%)	8,033 (12.61)	6,767 (11.49)	1,266 (26.28)	1163 (2.34)
Heart Failure (%)	916 (1.48)	628 (1.07)	288 (5.98)	63 (0.13)
Had an indication for an ACEi/ARB (%)	26,078 (40.92)	23,156 (39.31)	2,922 (60.65)	6,268 (12.61)
Were on an ACEi/ARB (%)	18,698 (71.70)	16,455 (71.06)	2,243 (76.76)	3,035 (6.12)
Had no indication for an ACEi/ARB (%)	37,644 (59.08)	35,748 (60.69)	1,896 (39.35)	43,427 (87.39)
Were on an ACEi/ARB (%)	5,236 (13.91)	4,751 (13.29)	485 (25.58)	1,095 (2.20)
On a Thiazide Diuretic (%)	12,628 (19.82)	11,384 (19.33)	1,244 (25.82)	2,796 (5.63)
On another Diuretic (%)	1,724 (2.71)	1,305 (2.22)	419 (8.70)	256 (0.52)
On a Calcium Channel Blocker (%)	17,744 (27.85)	15,785 (26.80)	1,959 (40.66)	2,488 (5.01)
On a Beta Blocker (%)	3,794 (5.95)	3,323 (5.64)	471 (9.78)	862 (1.73)
On an Alpha Blocker (%)	1,004 (1.58)	849 (1.44)	155 (3.22)	58 (0.12)
On a Centrally Acting Agent (%)	83 (0.13)	65 (0.11)	18 (0.37)	14 (0.03)
Proteinuria (at study start):				
None recorded (%)	35,752 (56.11)	33,504 (56.88)	2,248 (46.66)	35,014 (70.46)
Normal to Mildly Elevated (%)	22,552 (35.39)	20,945 (35.56)	1,607 (33.35)	13,342 (26.85)
Moderately Elevated (%)	4,473 (7.02)	3,732 (6.34)	741 (15.38)	1,065 (2.14)
Severely Elevated (%)	945 (1.48)	723 (1.23)	222 (4.61)	274 (0.55)

GFR (glomerular filtration rate), AKI (acute kidney injury), CKD (chronic kidney disease), ACEi (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker).

90 days of starting a RAS antagonist and at the percentage of those with AKIN1. In the first 90 days after initial RAS antagonist prescription only 194 instances fulfilled criteria for AKIN1 (4% of all AKIN1 in the study) representing only 2.5% of 7,765 blood test instances.

Table 2 shows the multilevel logistic regression results examining the association between RAS antagonists, and other variables, with AKI.

The results for all four models suggested that treatment with RAS antagonists was significantly associated with an increased risk of AKI. The size of the effect decreased after adjustments for potential confounders falling from a 93% increased risk in the unadjusted model to 69% after adjustment for age and gender and to 11% in the fully adjusted model. All of the confounding variables examined were significantly associated with AKI. There was an increased risk of AKI for patients with hypertension, diabetes, ischaemic heart disease (IHD), heart failure, worsening severity of CKD, proteinuria and diuretic therapy. Males were at an increased risk relative to females. There was a non-linear relationship between age and AKI, and thus it is easier to view the results graphically (Figure 2), the results suggesting that for patients aged less than 60 years there was no strong relationship between age and risk of AKI. In those aged 60 and above the risk increased exponentially. There

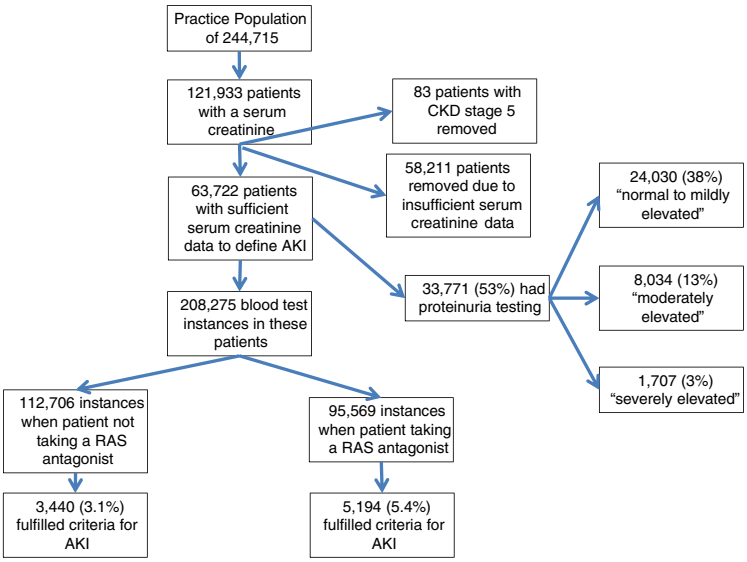

Figure 1 Study cohort and acute kidney injury (AKI) subdivided by RAS antagonist prescription and proteinuria testing.

was a non-linear relationship between systolic blood pressure and AKI, and thus again it is easier to view the results graphically (Figure 3). Both hypotension and hypertension were associated with an increased risk of AKI.

Table 3 shows the multilevel logistic regression results examining the association between RAS antagonists, and other variables, this time with AKIN2/AKIN3 or noAKI/AKIN1. Only the first 2 models (unadjusted 73% increased risk, age and gender adjusted 62% increased risk) suggested that treatment with RAS antagonists was significantly associated AKIN2/AKIN3. After adjusting for the remaining variables (models 3 and 4), there was no statistically significant difference in the occurrence of AKIN2/3 status between those taking and not taking ACE/ARBs. In this analysis only hypertension, systolic blood pressure, use of diuretics and presence of proteinuria of the confounding variables were significantly associated with AKIN2/AKIN3.

By indication

The analysis was then repeated with at each "blood test instance" an assessment made of whether there was an evidence-based indication for the prescription of a RAS antagonist, other than simple hypertension. The exception was proteinuria where the highest proteinuria result was used. Table 4 summarises the association between indication, RAS antagonist prescription and AKI subdivided by the two differing scenarios (no AKI versus AKI and no AKI/AKIN1 versus AKIN2/AKIN3).

This summary suggests a greater effect of RAS antagonists on AKI for patients prescribed RAS antagonists with no evidence-based indication. If there was an indication for RAS antagonist prescription then there was no real difference in the risk of AKI. In the patients prescribed RAS antagonists without an evidence-based indication there appeared to be an increase in the risk of AKI.

The multilevel logistic regression was then repeated to examine the effects of RAS antagonists on AKI in the groups with and without an evidence-based indication (Table 5), using only model 1 (unadjusted) and model 2 (adjusted for age and sex) of the previous four models described above. Model 3 and model 4 were not used as the presence of co-morbidities such as diabetes, heart failure etc. and the presence of proteinuria would by definition give the patient an indication for RAS antagonist prescription and hence both these variables and indication could not be corrected for in the same model. Terms for the indication of RAS antagonists and also an interaction term between this variable and the actual occurrence of RAS antagonist prescription were included in the model.

Analysis of the data in this was way suggested that there was a significant interaction between evidence-based indication and RAS antagonist use. In both models the risk of AKI was significantly higher with RAS antagonist use in both subgroups. However, the effects appeared greater in patients with no evidence-based indication.

Table 2 Multilevel logistic regression examining the association between renin angiotensin system antagonists and other variables with acute kidney injury

Variable	Category/term	Odds ratio (95% CI)	P-value
Model 1			
ACE/ARB	No	1	**<0.001**
	Yes	1.93 (1.81, 2.06)	
Model 2			
ACE/ARB	No	1	**<0.001**
	Yes	1.69 (1.58, 1.81)	
Age (*)	Linear term	0.41 (0.35, 0.48)	**<0.001**
	Quadratic term	1.12 (1.10, 1.13)	
Sex	Female	1	**<0.001**
	Male	1.70 (1.58, 1.83)	
Model 3			
ACE/ARB	No	1	**<0.001**
	Yes	1.17 (1.09, 1.25)	
Age (*)	Linear term	0.48 (0.42, 0.56)	**<0.001**
	Quadratic term	1.08 (1.07, 1.09)	
Sex	Female	1	**<0.001**
	Male	1.61 (1.450, 1.72)	
Hypertension		1.30 (1.17, 1.44)	**<0.001**
Diabetes		1.47 (1.37, 1.58)	**<0.001**
IHD		1.24 (1.16, 1.35)	**0.001**
Heart Failure		2.29 (2.04, 2.56)	**<0.001**
Systolic BP < 100		2.32 (2.09, 2.58)	**<0.001**
CKD stage	1	1	**<0.001**
	2	1.90 (1.76, 2.04)	
	3	3.79 (3.46, 4.14)	
	4	6.79 (5.93, 7.77)	
Diuretic		1.42 (1.34, 1.51)	**<0.001**
Model 4			
ACE/ARB	No	1	**0.01**
	Yes	1.11 (1.02, 1.20)	
Age (*)	Linear term	0.69 (0.55, 0.87)	**<0.001**
	Quadratic term	1.05 (1.03, 1.06)	
Sex	Female	1	**<0.001**
	Male	1.51 (1.40, 1.64)	
Hypertension		1.36 (1.18, 1.56)	**<0.001**
Diabetes		1.13 (1.04, 1.23)	**0.004**
IHD		1.28 (1.17, 1.40)	**<0.001**
Heart Failure		2.10 (1.85, 2.38)	**<0.001**
Systolic BP < 100		2.28 (2.01, 2.59)	**<0.001**
CKD stage	1	1	**<0.001**
	2	1.82 (1.67, 1.99)	
	3	3.40 (3.06, 3.77)	
	4	5.12 (4.38, 5.99)	
Diuretic		1.45 (1.35, 1.56)	**<0.001**
Proteinuria	None	1	**<0.001**
	Moderate	1.83 (1.69, 1.99)	
	Severe	3.27 (2.87, 3.72)	

(*) Odds ratios given for a 10-unit increase in the explanatory variable. Odds ratios describe the effect of all variables upon the outcome. For variables measured on a categorical scale, the odds ratios represent the odds of AKI in each category relative to a baseline category. For the continuous variables, the odds ratios represent the change in the odds of AKI for one-unit increase in that variable. A series of four models were examined, each considering the effects of RAS antagonists with different combinations of adjustments for other variables. Model 1 was unadjusted, model 2 was adjusted age and gender, model 3 for all variables apart from proteinuria and model 4 for all variables. CKD (chronic kidney disease), ACE (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker), IHD (ischaemic heart disease), BP (blood pressure).

Discussion

Where there is an evidence-based indication for RAS antagonists over and above simple hypertension the literature suggests clear benefits in terms of reduction in all cause and cardiovascular mortality, progression of CKD and reduction in proteinuria [1-3]. Our study demonstrates an increased risk of AKI occurring in primary care in all patients prescribed RAS antagonists even after multiple adjustment for confounding risk factors, importantly including adjustment for systolic blood pressure. However, that risk becomes much lower in the fully adjusted model and when the analysis was repeated for moderate and severe AKI there was no increased risk associated with RAS antagonist prescription in the fully adjusted model. Furthermore, when analysed by evidence-based indication for RAS blockade, although there was no increased risk of AKI in those prescribed RAS antagonists with an indication, in patients prescribed RAS antagonists without an evidence-based indication the risk of AKI was significantly increased. This raises the question of whether or not risk outweighs benefit where there is no indication for RAS antagonist prescription over and above simple hypertension. We know from published data that all stages of AKI, even AKIN1, confer an increased risk of adverse outcome [15-23].

In high risk situations such as cardiac surgery the risk of AKI in those prescribed RAS antagonists preoperatively is significantly increased, by 27.6% in one study [24]. There are surprisingly few studies that have specifically addressed the risk of AKI in all patients prescribed RAS antagonists, and our study is the first to attempt to examine this by evidence-based indication. A recent ecological analysis suggested that up to 15% of the increase in AKI admissions in England over a 4-year time period was potentially attributable to increased prescribing of RAS antagonists but these findings were limited by the lack of patient level data including indication for

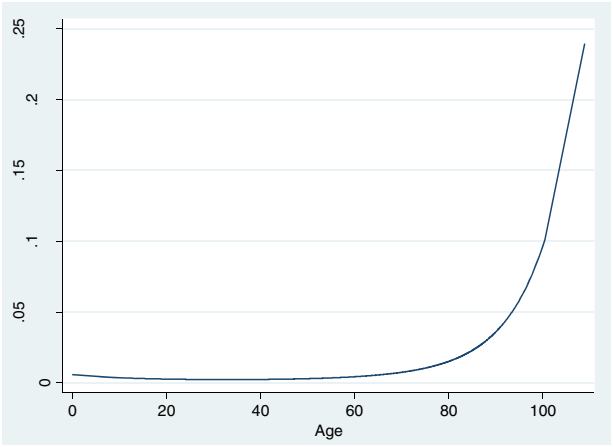

Figure 2 Relationship between age and the probability of AKI.

prescribing and patient characteristics [25]. Lapi and colleagues examined the risk of AKI associated with the concurrent use of diuretics, RAS antagonists and non-steroidal anti-inflammatory drugs (NSAIDs) in a nested case–control study. They reported that the triple therapy combination consisting of diuretics RAS antagonists and NSAIDs was associated with an increased risk of AKI but that dual therapy combinations were not [26]. Harel et al. conducted a systematic review of published and unpublished RCTs that provided numerical data on adverse event outcomes, including AKI, when comparing monotherapy or combined treatment with different classes of RAS antagonists. The risk of AKI (defined as a serum creatinine concentration greater than 176.8 μmol/L) was no greater with combination therapy versus monotherapy [27].

Why is it that we find an increased risk of AKI in those prescribed RAS antagonists in the absence of an evidence-based indication, but not in those with an indication for prescription? It is likely that this relates to the relative contribution of confounding variables to risk of AKI. When we examined the risk of all AKI conferred

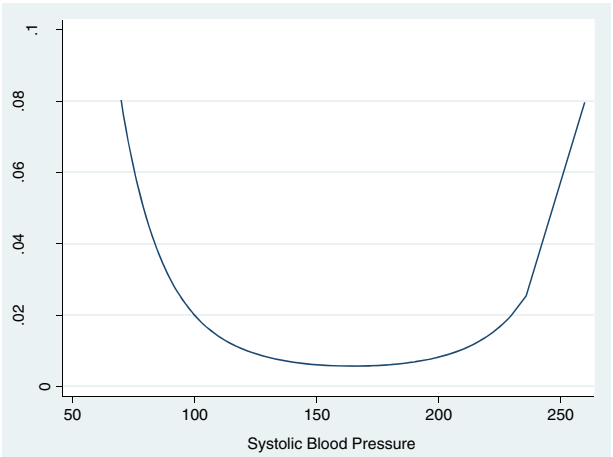

Figure 3 The relationship between systolic blood pressure and the probability of AKI.

Table 3 Multilevel logistic regression examining the association between renin angiotensin system antagonists and other variables with AKIN2/AKIN3 compared with noAKI/AKIN1

Variable	Category/term	Odds ratio (95% CI)	P-value
Model 1			
ACE/ARB	No	1	**<0.001**
	Yes	1.73 (1.41, 2.11)	
Model 2			
ACE/ARB	No	1	**<0.001**
	Yes	1.62 (1.31, 1.99)	
Age (*)	Linear term	0.44 (0.30, 0.67)	**<0.001**
	Quadratic term	1.09 (1.06, 1.13)	
Sex	Female	1	0.21
	Male	1.15 (0.92, 1.43)	
Model 3			
ACE/ARB	No	1	0.85
	Yes	1.02 (0.81, 1.29)	
Age (*)	Linear term	0.43 (0.27, 0.68)	**<0.001**
	Quadratic term	1.08 (1.04, 1.12)	
Sex	Female	1	0.34
	Male	1.12 (0.89, 1.40)	
Hypertension		1.87 (1.27, 2.74)	**0.001**
Diabetes		1.69 (1.33, 2.15)	**<0.001**
IHD		0.96 (0.73, 1.25)	0.75
Heart Failure		2.09 (1.44, 3.05)	**<0.001**
Systolic BP < 100		4.37 (3.18, 5.99)	**<0.001**
CKD stage	1	1	**<0.001**
	2	1.32 (1.01, 1.71)	
	3	1.78 (1.29, 2.45)	
	4	2.39 (1.47, 3.91)	
Diuretic		1.66 (1.34, 2.06)	**<0.001**
Model 4			
ACE/ARB	No	1	0.17
	Yes	0.83 (0.63, 1.09)	
Age (*)	Linear term	0.47 (0.24, 0.93)	**<0.001**
	Quadratic term	1.07 (1.02, 1.12)	
Sex	Female	1	0.79
	Male	1.06 (0.81, 1.40)	
Hypertension		2.17 (1.29, 3.65)	**0.003**
Diabetes		1.32 (0.99, 1.74)	0.06
IHD		1.07 (0.78, 1.46)	0.69
Heart Failure		1.66 (1.07, 2.56)	**0.02**
Systolic BP < 100		4.34 (2.96, 6.36)	**<0.001**
CKD stage	1	1	0.47
	2	1.16 (0.85, 1.56)	
	3	1.31 (0.89, 1.92)	
	4	1.38 (0.76, 2.45)	
Diuretic		1.56 (1.20, 2.02)	**0.001**
Proteinuria	None	1	**<0.001**
	Moderate	1.62 (1.21, 2.17)	
	Severe	3.43 (2.22, 5.29)	

AKI (acute kidney injury), AKIN1 (acute kidney injury network stage 1), AKIN2 (acute kidney injury network stage 2), AKIN3 (acute kidney injury network stage 3), sCKD (chronic kidney disease), ACE (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker), IHD (ischaemic heart disease), BP (blood pressure).
(*) Odds ratios given for a 10-unit increase in the explanatory variable.

by prescription of RAS antagonists that risk fell when adjusted for confounding variables and there was no increased risk of moderate to severe AKI after adjustment. We conjecture that because significant comorbidities such as systolic hypotension, heart failure and proteinuria are absent in those without an evidence-based indication for RAS antagonists prescription the contribution of RAS antagonism in such patients is that much more significant. There may also be a lower level of awareness and monitoring in those with fewer co-morbidities.

Our study has limitations. The study cohort is derived from the primary care population with recorded serum creatinine estimations. Although serum creatinine tests were recorded in 50 percent of the whole primary care

Table 4 The association between evidence-based indication, prescription of renin angiotensin system antagonist and acute kidney injury

Indication for ACE/ARB	ACE/ARB	No AKI	AKI
		N (%)	N (%)
No	No	83,724 (97.8%)	1,846 (2.2%)
	Yes	18,331 (96.2%)	721 (3.8%)
Yes	No	25,542 (94.1%)	1,594 (5.9%)
	Yes	72,044 (94.2%)	4,473 (5.8%)
No AKI/AKIN1 versus AKIN2/AKIN3			
Indication for ACE/ARB	ACE/ARB	No AKI/AKIN1	AKIN2/AKIN3
		N (%)	N (%)
No	No	85,428 (99.83%)	142 (0.17%)
	Yes	18,989 (99.67%)	63 (0.33%)
Yes	No	27,032 (99.62%)	104 (0.38%)
	Yes	76,267 (99.67%)	250 (0.33%)

AKI (acute kidney injury), AKIN1 (acute kidney injury network stage 1), AKIN2 (acute kidney injury network stage 2), AKIN3 (acute kidney injury network stage 3), CKD (chronic kidney disease), ACE (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker), IHD (ischaemic heart disease), BP (blood pressure).

Table 5 Multilevel logistic regression examining the association between renin angiotensin system antagonists and acute kidney injury by evidence-based indication (model 1 shows the effects of renin angiotensin system antagonists with no adjustment, model 2 is adjusted for age and gender)

Model	Interaction p-value	Indication	Odds ratio (95% CI)	P-value
No AKI versus AKI				
Model 1	<0.001	No	1.94 (1.72, 2.19)	**<0.001**
		Yes	1.14 (1.04, 1.24)	**0.004**
Model 2	0.003	No	1.52 (1.34, 1.72)	**<0.001**
		Yes	1.22 (1.12, 1.33)	**<0.001**
No AKI/AKIN1 versus AKIN2/AKIN3				
Model 1	<0.001	No	2.31 (1.61, 3.30)	**<0.001**
		Yes	0.98 (0.74, 1.30)	0.90
Model 2	0.005	No	2.04 (1.41, 2.94)	**<0.001**
		Yes	1.05 (0.79, 1.39)	0.73

AKI (acute kidney injury), AKIN1 (acute kidney injury network stage 1), AKIN2 (acute kidney injury network stage 2), AKIN3 (acute kidney injury network stage 3).

population serum creatinine testing in primary care is not random. People with diabetes, hypertension and cardiovascular disease are over represented within our serum creatinine sample. In just under half of the population with serum creatinine estimations there were no baseline data to determine the risk of AKI and these patients could not be considered further. However, in the data analysed the absolute number of serum creatinine tests in those prescribed RAS antagonists was not dissimilar to the number in those not prescribed RAS antagonists. Furthermore those with no baseline data to determine risk of AKI were significantly younger with very little co-morbidity and only 5 percent had CKD. In this analysis we could not determine absolute risk of AKI and it is also important to note that the analysis only included blood tests from primary care, and therefore there is the possibility that we have not accounted for episodes of AKI that were managed in hospital and from which no blood tests were recorded in primary care. This is however a potential strength, as this excludes hospital acquired AKI and possible additional confounders. Another limitation is in the prescribing assumptions. Although primary care databases record the prescription of a drug the quantity given is often not available, and this may range for example from 1 – 3 months. We therefore made the assumption that if the last prescription date was within 70 days of the "blood test instance", then the patient was still receiving the medication at that time. Although we were able to include diuretics in the analysis we were unable to accurately define the impact of non-steroidal anti-inflammatory combinations with other agents on the risk of AKI and therefore did not include this in the analysis.

Whilst there may be inaccuracies in database coding of co-morbidities individual patient level co-morbidity coding in primary care databases has been shown to be accurate, allowing correction for a number of known confounders in our analysis [28]. The introduction of the Quality Outcomes Framework, a pay for performance system in primary care in the United Kingdom, is likely to have further improved co-morbidity recording as targets for chronic disease management have been implemented [29].

This data set is also subject to survival bias in that people who live longer may contribute more tests to the analysis. Another potential source of bias was a misdiagnosis of AKIN1 purely as a result of change in serum creatinine following introduction of RAS antagonists. However, only 4% of AKIN1 occurred within 90 days of starting treatment with a RAS antagonist making this an unlikely source of significant bias.

This is the first study that identifies the risks associated with the indiscriminate use of RAS antagonists in a large general population cohort. For the first time we present data concerning the potential adverse effects of RAS antagonists in patients without a clear evidence-based indication for their use other than simple hypertension. Inclusion of all adults is a particular strength as older people are largely under-represented in randomised controlled trials of RAS antagonists and the incidence of AKI rises exponentially with age. A further strength of the study is the access to complete prescription data because primary care in England records all prescription data electronically.

Use of RAS antagonists independently predicted AKI in the multivariate analysis and it should be noted that in people with no evidence-based indication for treatment with RAS antagonists the risk of AKI was significantly increased. There will always be disease groups where the benefits of treatment with RAS antagonists clearly outweigh the risks, however we submit that treatment with these agents should be restricted to people in

whom there is a clear evidence-based indication. Given the increasing incidence of AKI with increased age this is especially important in older people.

Strategies to mitigate the risk of AKI in people prescribed RAS antagonists should be encouraged, including regular monitoring of kidney function and the use of tablet holidays during intercurrent illness, especially that likely to involve intravascular volume depletion.

Conclusion

In conclusion the use of RAS antagonists increased the risk of mild AKI in the community in this analysis and was independent of common confounding variables including age, baseline kidney function, gender, relevant co morbidities and systolic blood pressure. The risk of moderate to severe AKI was also increased by prescription of RAS antagonists but was no longer significant when fully adjusted for confounders. However, where there was no evidence-based indication for use of RAS antagonists the risk of mild, moderate and severe AKI remained significantly increased.

Competing interests

The authors declare that they have no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Authors' contributions

MB, PS, JI and CF all contributed to data extraction and analysis and preparation and revision of the manuscript. All authors read and approved the final manuscript.

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Appendix 5: Qualitative analysis documentation

Data Analysis Framework

Introducing the AKI Alert System	
Analytical construct	***Quote and code***
Coming to know about the AKI Alert System	
Introduction to the system, how this happened	
Preparation for use, training	
Length of time system used	
How introduction could be improved	
Other	
Using the Technology	
General experiences of using the technology	
Accessibility	
Ease of navigation	
Visual impact	
Opinions of information on the system	
Ease of identifying cohort	
Relevance of information	

Accuracy	
Sufficiently up-to-date	
How information is used	
Accessing information	
Communicating information	
Monitoring behaviour	
Influencing treatments/interventions	
Communicating to clinician looking after the patient	
Strengths of technology	
Weaknesses of technology	
Improvements to technology	
Other	
Impacts on Clinical Practice and Patients: consultants	
Changes to clinical practice from the AKI Alert System	
Positive changes	
Negative changes	
Communicating to teams	

Team's understanding of acute kidney injury	
Difference to patient care	
Positive differences	
Negative differences	
Added value, cost-effectiveness	
Other	
Impacts on Clinical Practice and Patients: nurses	
Changes to clinical practice from the AKI Alert System	
Positive changes	
Negative changes	
Assessment behaviour	
Explanation of disparities between areas	
Working with medical teams	
Communication issues	
Reactions to requests	
Response to referrals	

Other	
Comments/suggestions for improvement/other	

Evaluation of the AKI Alert System to identify and monitor patients with Acute Kidney Injury (AKI): Consultant Interview

1 Introducing the AKI Alert System

a) How did you first come to know about the AKI Alert System?
Prompts: who introduced the system, where, preparation for use/training received, how long using it?

b) What were your initial reactions?

c) How could your introduction to the system have been improved?

2 Using the technology

a) Describe to me your experiences of using the technology
Prompts: accessibility, ease of navigation, visual impact, strengths and weaknesses

b) Tell me about your opinions of the information on the system.
Prompts: ease of identifying cohort, relevance of information, accuracy, sufficiently up-to-date, strengths and weaknesses?

c) How do you use this information?
Prompts: how often accessed, communication of information, monitoring behaviour, treatment/interventions? Communicating to clinician looking after the patient?

d) Do you have any suggestions for how the technology could be improved?

3 Impacts on clinical practice and patients

a) Does the AKI Alert System change clinical practice?
Prompts: examples of positive and negative changes to clinical practice.

b) Tell me about how you communicate with the clinical teams looking after the patient.
Prompts: What do they know about AKI? Any difficulties with communication?

a) Can you think of any ways that it makes a difference to patient care?
Prompts: positive and negative differences, does it add value, is it cost-effectiveness?

4 Any other comments or suggestions for improvement?

Outreach Nurse Focus Group Schedule

Evaluation of the AKI Alert System to identify and monitor patients with Acute Kidney Injury (AKI): Outreach Nurse Focus Group

1 Introducing the AKI Alert System

d) How did you first come to know about the AKI Alert System?
Prompts: who introduced the system, where, preparation for use/training received?

e) What were your initial reactions?

f) How could your introduction to the system have been improved?

2 Using the technology

e) Describe to me your experiences of using the technology
Prompts: accessibility, ease of navigation, visual impact, strengths and weaknesses

f) Tell me about your opinions of the information on the system.
Prompts: ease of identifying cohort, relevance of information, accuracy, sufficiently up-to-date, strengths and weaknesses?

g) How do you use this information?
Prompts: how often accessed, communication of information, monitoring behaviour, treatment/interventions?

h) Do you have any suggestions for how the technology could be improved?

3 Impacts on clinical practice and patients

b) Has the AKI Alert System changed the way you work?
Prompts: examples of positive and negative changes to clinical practice, assessment behaviour (disparity in assessments per area – why?)

c) Tell me about your experiences of working with members of the medical team. *Prompts: communication issues, reactions, responding to referrals?*

d) Are there any specific impacts from a professional viewpoint?
Prompts: should patients with AKI be a focused part of the job, or just an addition to support the renal team? Will this become embedded in the future role of outreach nurses?

e) Can you think of any ways that it makes a difference to patient care?
Prompts: positive and negative differences, added value, cost-effectiveness?

4 Any other comments or suggestions for improvement?

Appendix 6: Results of a qualitative analysis of clinical alerting and clinical intervention

This report describes the findings of the individual interviews with renal consultants and the focus group with outreach nurses from critical care conducted approximately 18 months following the introduction of the SAKI AKI alert system. The purpose of this facet of the study was to ascertain perceptions of the system, interaction with the technology, communication with medical teams, impacts on patients and clinical practice, and recommendations for improvements.

This report was compiled by Professor Jenny Billings (Professor of Applied Health Research, University of Kent) with assistance from Dr Michael Bedford.

Table 43 below lists the main themes and sub-themes emanating from the data. Quotes from the respondents are used in the analysis to justify interpretation, with 'C' referring to a consultant response and 'ON' referring to an outreach nurse response. Further numerical coding refers to the interviewee code for the respondents and the page number of the transcript from where the quote was derived. To give an example:
C3:4 = Consultant 3, transcript page 4.

The AKI alert system at EKHUFT when assessed was delivered through Qlikview, a browser based reporting tool, hence references in quotes referring to "Qlikview" are referring to the AKI alert system.

Each section of the analysis is followed by a short summary, highlighting the main points raised.

Table 43: Analytical themes and sub-themes emanating from the qualitative analysis

Themes	Sub-themes

1 Introducing the alert system	1.1 Getting to know the alert system 1.2 First reactions to the system
2 Using the technology	2.1 General comments 2.2 Issues with user-friendliness 2.3 Timing and workload 2.4 Accessing data and making decisions
3 Interacting with medical teams	3.1 Finding the right doctor 3.2 Discussing the cases 3.3 Awareness of the alert system
4 Monitoring cases	4.1 To follow up or not to follow up? 4.2 Acting on advice
5 Impacts on patient care and clinical practice	5.1 Making a difference to patient care 5.2 Impacts on clinical practice 5.3 Perceptions of cost-effectiveness
6 Recommendations for improvements	6.1 Improving Trust-wide knowledge of the alert system 6.2 Improving the technology

1 Introducing the Alert System

This first theme focuses on perceptions of how respondents first heard of the alert system, were instructed how to use it, and their initial reactions to becoming part of the system.

1.1 *Getting to know the alert system*

Some respondents had already used a similar system so found the transition to using it for the research straightforward:

> I've used Qlikview already so I'm familiar with it...[researchers] took me through the system and I basically got on with it. (C6:1)
>
> .... I'd used Qlikview previously, some of the Trust data's on Qlikview itself.... I think [researcher] probably discussed it at one of our senior doctor meetings and then it was introduced, and we'd had a chat about using it....that the on call consultant would use it every day to identify patients. (C4:1)

> I basically was using it in a previous job role...to access A&E data so we was [verbatim] kind of familiar with it from there. And then ... I've just adapted the bits of it that I'm using really (ON2:1)

The nature of the first introduction appeared to be informal and brief, with some having difficulty remembering:

> I think it was at a meeting that [researcher] briefly mentioned but it wasn't a formal you know, unveiling of the system... (C1:2)
>
> I don't think there was any formal training that I remember, just opened it and started using it. (C3:1)
>
> I can't remember actually..... I suppose [researchers] must have shown us, shown me how to use it but I honestly can't remember. (C2:1)

The outreach nurses appeared to have had more formal training which they rated highly in terms of meeting their needs, and particularly valued the accessibility of the researcher:

> ... when [researcher] trained us, I certainly felt that it was very adequate. We had several sessions with him. And I feel very much that if I needed anything I could always get what I wanted from [researcher] so it wasn't ... it wasn't just an informal thing for us. (ON1:4)
>
> I mean [researcher] is very adaptable and approachable in terms of giving us what we need, I think, as a whole team across the sites in terms of education and updates and stuff. (ON3:4)

Some of the consultants had already been involved in its conception so were knowledgeable about it from the start, as explained here:

> I was aware of its development and you know [researcher] would talk about it whilst it was being developed and ask for ideas and suchlike... (C5:2)

Most respondents felt the system was relatively straightforward and were able to learn experientially, without the need for more formal training:

> ... a lot of it was sort of learning as you tried to use the system, you try ... and you learned how to access this bit of it or that bit of it ... (C1:1)
>
> ... it's not very complicated, but yes we were given passwords for access to Qlikview and the AKI system and then I think [researcher] took a quick whizz through and that was it. (C5:1)

... you learn the tricks as you go, so I think expectations of how you're taught how a system works are probably too high ... the practicalities of doing it - actually that experience is quite a useful tool. (C4:3)

1.2 First reactions to the system

All respondents appeared keen to support colleagues and welcomed the alert system. There was also an acknowledgement of its importance and potential contribution to innovation and change in renal medicine:

... well I thought it was a good idea because we I mean we have been doing this with chronic kidney disease and advising GP practices so I thought with acute kidney injury ... it was quite a good idea and I was keen to continue with it and help out the research process. (C1:1)

I think it's great that there's a system in place to pick people up. (ON4:26)

It's important work, not only for the Trust but it fits with the recommendations of the NCEPOD report for AKI ... and the general Department of Health research and innovation agenda....yeah, so good for patients and practice. (C6:1)

Following from the last quote, other respondents also recognised how the system could improve patient care and impact on practice, but also visualised the proactive nature of the alert system in bringing this about:

... people can be going 'off' without anybody realising, so having an alert system that actually picked it up and prompted the doctors looking after them to actually have a think about what might be going on with this patient seemed like a very good idea. (C5:1)

... it's our only means of identifying some of the sick patients ... and quite often some of these groups of patients we will only pick up on because they've been identified through the alert system. ... Had we not had that access to that we probably would never even know they're in hospital. (ON2:5)

... well I think it's a very good idea ... I think is very important and using the benefits of the expertise that we have in the Trust for building these platforms I think makes a lot of sense, I'm enthusiastic. (C2:1)

One respondent however did feel a sense of imposition; this quote suggests that there was little choice:

> ... we were told that we had to start using it, we were told that it was part of a research and that they were trying to sort of incorporate it into our normal daily activities and practice. (C1:1)

The outreach nurses also collectively had some reservations due to the added workload and goodness of fit with their role, an aspect elaborated upon later:

> I'm not sure we were totally warm to it because it was just something else to add to our job ... And we've got one of those umbrella jobs where we ... 'Outreach will do it anyway' ... And then it was like *oh.* But ... it is quite appropriate to see the patients very often because they're sick and they have renal failure ... But we weren't exactly, "Yay!" (ON1:4/5)
>
> I ... I sort of personally queried why this wasn't being taken up by the renal satellite unit ... and I did feel a little bit *well I'm not quite sure that that's appropriate for us.* (ON3:5)

1.3 Summary

Initial responses to the alert system appeared to be encouraging. There was strength of opinion regarding the desire to support colleagues and the research endeavour, and an understanding of its potential contribution to renal medicine. Given that the alert system has been in operation for nearly two years, these sentiments expressed by most respondents appeared to be enduring, evidenced by their use of the present tense when describing their views. Alongside this, there was however a tendency for the outreach nurses to greet the system with a degree of uncertainty regarding their roles. Outreach nurses had more formal training which they appreciated, and although seemingly brief and informal for the consultants, the induction process appeared sufficient to engage colleagues as the technology was not complex.

2 Using the Technology

Theme two explores opinions and use of the system technology, and includes a general overview of accessibility and functionality, followed by a deeper analysis

of issues concerning user-friendliness, timing and workload, and factors relating to accessing data and making decisions.

2.1 General comments

General comments about the technology are summarised by the quotes below and included opinions about accessibility to information and the population group:

> I think the accessibility is good, the fact that it's web based so you don't have to have software installed on a specific computer and the fact that I can access it from my ipad at home ... I don't have a problem with it, it's quite intuitive, visual impact you know that's fine again. (C2:3)
>
> I use it really just to identify the patients with AKI 3 and those who have not had intervention ... I only deal with the ones who have not had any comments, so the new ones. (C4:5)

With respect to its overall functionality, a frequent comment related to how respondents restricted their use to certain features deemed most relevant:

> ... there are a lot of buttons at the top but I never use most of them ... most of the information is, the important things, that they've got AKI 3, where they are and what team they're under... (C4:8)
>
> I appreciate that there are a lot of tabs along the top that I just haven't explored really through lack of time more than anything else but in terms of the core functionality it's very easy to use. (C2:1)
>
> To be honest I only access the first page and then I go into other systems because they provide for more information. (C5:4)

2.2 Issues with user-friendliness

More detailed exploration with respondents highlighted a number of issues regarding the ease or difficulty of navigating the system and accessing data. These following quotes describe the main difficulties experienced. Firstly, the speed and responsiveness of the system appeared problematic:

> ... sometimes the pages wouldn't load and if you were trying to filter out things it wouldn't, it would take a while to ... get to the filter page which you

wanted to look at so sometimes a lot of clicking and logging out of the system and logging back onto it ... (C1:2)

The system is very variable in terms of it does seem to not want to upload or refresh and stuff quite regularly. (ON2:20)

... there's a way you can add comments so that your colleagues for the following day know that you've already sort of dealt with that patient and that can be a little bit sluggish to upload ... (C6:4)

The 'modernity' of the system was also commented on by one respondent:

... it's not very pretty ... because actually we're used to doing most stuff on webpages then you go to Amazon or whatever else you know that's what we're used to, and it's a very different system and I don't think it's knowledge user friendly. (C4:9)

The mechanisms through which identifiable patient data could be retrieved and information added also raised issues:

... sometimes just when you start, when you log in you have to clear all the selections and then start again otherwise you don't get all the patients quite right ... you might miss patients. (C4:4)

... if you were reporting on a certain patient you have to manually enter sort of details, for example the NHS number or whatever and that was a bit time consuming ... (C1:2)

... it's been hard to be able to print... off the lists and then when I've gone back at the end of the day to try and put something in I get locked out again or not being able to log in. (ON4:20)

if you're documenting in notes, on a handover sheet ... then try and do it on the Qlikview as well and you think... It's an endless process. (ON2:20)

Given that the system was in development, the research team appeared responsive to some of the difficulties respondents were experiencing:

Things that [researcher] has changed which I like is that now it actually updates more quickly when you actually fill in a form and that information goes in there much more quickly now. (C5:2)

2.3 Timing and workload issues

While, overall, respondents appeared keen to participate, a further theme to emanate concerned the amount of time it took to use the alert system. These following quotes from a consultant and an outreach nurse respectively summarise the different patterns of system use and associated activity:

> … an average month about three times, and then when you're on the wards, which is one month every fourth month you're on the ward, then actually on top of that three you'll do two weekends so you'll access it another six times that month. (C5:6)

> ... [we access it] Every day. And then we look at the people that are scoring twos and maybe threes. We, you know, we don't exclude the threes because they might not have been enquired about at the point that we go. (ON3:7)

Consultants were particularly keen to highlight the relationship with workplans. Every time they are on call, they encountered between one to eight new cases of AKI Stage 3. While this respondent appeared reconciled to accommodating the work ...

> You just incorporate it into your workplan ... yes, other things get pushed down the list but it's swings and roundabouts. (C6:4)

... most found the integration of this additional work troublesome in that it was not officially incorporated into their workplans:

> ... there's been no time put in my job plan to do it ... it depends on the day but often it's quite a burden ... (C5:7)

> ... you need a good one and a half to two hours of just you and the computer and the phone ... I think that it needs to be accounted for ... I think because it's a big chunk of work that we have to do ... (C1:5)

Following on from this, others had difficulty prioritising the work, particularly as there was a significant time commitment; reasons for this are explored more fully in a later section:

> ... trying to fit it in there was very difficult and it didn't always happen to be perfectly honest and I used to slightly resent it then but there you go, just one of those things. (C2:4)

> … a lot of time is wasted especially when you're on call and you have to have other things you know, if you have got a ward round that day, clinic that day, so it takes time. (C3:3)

... we've all got lots of other things going on and ok it's only once every ten days so it's not that often but it's just a bit irritating having to do it ... (C4:8)

2.4 Accessing data and making decisions

An issue of concern related to the fact that the data on the alert system provided information that was up to 24 hours old and this posed problems for where the patients were located, the uncertainty of their medical condition and the time that was wasted:

… sometimes the ward has changed ... you have to go on some other system to find where exactly the patient is and sometimes you have to, when we ring a ward they say, well, they've moved to the other one. (C3:4)

... a lot of the time the results will be from A&E and they'll flag up on Qlikview from A&E so you think *I'll go into the computer system and track a patient. Oh where are they now on the site* you know. You'll trawl all the way over there to find out they've just had their bloods done and their result's better so you've wasted like half an hour. (ON2:18)

… you are in a way acting on yesterday's data so you're coming in up to twenty-four hours later when a lot more things would have happened to that patient in the time period, which is a small problem I think. (C1:3)

There was a view among some respondents that this time lag had its advantages:

I'm not sure true real time would be a necessary advantage actually ... because I think that twenty-four hours of hindsight allows certain things to sort themselves out … the patient that's admitted clearly dying ... and me phoning up the team looking after them and saying this patient's got acute kidney injury … would probably not serve any useful benefit to either the patient or the team. (C2:3)

So there's somebody who's flagged up as [AKI stage] three, but the team have already started treating and if you can wait till the results are back you might see that their results are already improving, so ... it's sort of a good thing … (C4:4)

Respondents described in more detail how patients with AKI were identified and how decisions were made to formalise the alert and contact relevant teams. Given the time lag, it was clear that other datasets were needed to support the

decision-making process, as the alert system provided a first level identification of patients only such as NHS number, AKI stage and the ward:

> … you would have to log on to other systems ... the i-soft system, to sometimes look at the past clinical history from clinic letters and you'd also have to log onto the x-ray system to look at the current images and the historical images. (C1:3)
>
> ... I use all the other Trust IT systems ... so PAS to identify where they are ... and you can get in and use the blood results system either on that or DART to see what the latest result is and also the new VitalPac system I'll look up their observations and things ... you know you have to go and find it, yeah you have to open it up ... there's no link directly onto Qlikview. (C4:5)
>
> ... we can also look on the clinical functions at previous documents where they might have been to clinics so you can get a bit of a background but not all patients have those updated. (ON3:22)

For some this was frustrating, and this outreach nurse summed up the general feeling among the nurses:

> None of these systems interact with each other and it's just a nightmare really. (ON3:20)

While having all the data in one system was preferred, the view was that this was not too much of an imposition:

> I suspect it would be quite complicated to put interfaces with other systems so I think it, the other information is easily accessible on the net so it's not too complicated to access it ... I would say it probably takes me five or ten minutes to look at all the systems and formulate an opinion as to what might be going on with the patient before I try to ring them ... (C5:5/7)
>
> … the system identifies the patients, that's the crucial bit yeah I can access the other information, oh it's on another, I have to click another box and put in another password or whatever, but yes it's not the end of the world … (C6:6)

2.5 Summary

With respect to using the technology, most respondents restricted their use to a few of the alert system function, necessary for them to identify the AKI patients

and initiate the alert to medical teams. There were a number of factors relating to its lack of user-friendliness with regard to the sluggishness of navigating the system and inability to access data, and consultants raised the issue of increased workloads that was not built into workplans. While some felt able to assimilate this extra work, a number felt this to be quite onerous. Much discussion focused on the need to access data from other sources to facilitate decision-making about whether or not to alert the medical team, and the pros and cons of having a system that provided data that was 24 hours out of date.

3 Interacting with Medical Teams

A prominent issue for all respondents was accessing and interacting with medical teams to action the alert. This third theme describes how respondents tracked down the appropriate doctor, the differing experiences with communicating and discussing the cases, and the extent to which respondents felt that medical teams were aware of the alert system.

3.1 Finding the right doctor

Consultants in particular described this as a 'chasing game' that was frustrating, took up valuable time, and tried their patience. The quotes below elaborate on typical communication attempts in detail, focusing on difficulties tracking junior doctors and the 'tyranny' of bleep identification:

> ... the main problem ... is mapping junior doctor or junior doctor team to an individual patient and I think that work wasn't sufficiently developed before the system was rolled out ... a patient is flagged up as having AKI you then have to ... go through switchboard to identify which junior doctor is looking after the patient, you may phone the ward where ... you get given one bleep number, it turns out not to be the right bleep number ... and then that person doesn't answer that bleep and so you try a different member of the team and you know it can take half an hour to get hold of the right junior doctor and that's not an exaggeration ... that actually gets very tedious when you've got lots of other stuff to do to be bleeping about five different people before you get a response and I think that's a fairly common issue with it. (C2:2)

> And we have this daft system in this Trust where the [junior doctors] look after the wards at a weekend but because they're not actually on call ... the switchboards don't carry their bleep number ... they haven't got any number for them so you have to ring up the on-call team to actually ask them which [junior doctor] is on for the weekend and what bleep are they carrying. (C5:11)

> ... it's teams, and it's partly because teams are so unstable because the registrar's on holiday, the SHO's just done nights so it's only the house officer and actually they're in the middle of a ward round for a different team ... that is the big problem. (C4:12)

For all respondents, the frustration of trying to find the team responsible for the patient was clear, and the alert system did not appear to help in this regard:

> I mean you can't get hold of the right person, the person you eventually get hold of does not know the patient … you know the conversation doesn't take very long, it's just getting hold of people and whether they know about it or not. (C3:3)

> You deal with it generally out of hours by contacting a doctor who's not really responsible for that speciality of patient who is already generally busy and probably overworked so it's not an ideal system. (ON2:12)

> ... that's the real downside of this, I don't actually mind any of the other bits but I get so frustrated about trying to actually pin down somebody who actually knows something about this person who's willing to take responsibility and take it forward ... (C5:8)

> Very difficult. Very difficult. I think there was a thing, a page where you could look at the contact details of the teams and sometimes I cannot access that information from the actual Qlikview dashboards. (C1:5)

There were added difficulties when the patient was admitted through Accident and Emergency (A&E) ...

> ... trying to identify which team you're meant to be talking to when it's an A&E patient, so somebody comes in with AKI 3 into A&E, it'll flag up as A&E and then you have to track them down which is, I mean it's possible using the other IT systems but it's just a bit frustrating ... (C4:5/6)

... and when trying to contact certain specialities:

> ... surgery – particularly orthopaedics they, you can ring around quite a number of F2s [junior doctors] before you actually find someone who'll take responsibility or go and see the patient. (C5:7)

> ... what you need to do is get the best person that's going to give the best treatment to that patient and generally unfortunately that's not always the orthopaedic doctor. (ON2:13)

One respondent felt that the European directive on working time contributed towards these difficulties:

> ... what I've noticed is, you know, numbers of junior teams who don't know their patients because they weren't on call or they weren't, you know, or they were on a different ward round ... it's European working time that's mucked the whole thing up. (C4:6/7)

One respondent felt that more Trust-wide communication at the beginning of the project would have been better:

> I think it probably wasn't fully sorted out and like anything you introduce a system and actually you have to anticipate there's going to be problems and there will be a grumpy clinician somewhere who gets a bit silly about it all ... (C4:2)

Respondents had adapted to these difficulties by developing a range of strategies to improve their chances of accessing the right doctors:

> ... usually I get hold of the right person straight away by actually phoning the ward … I guess then that reflects the fact that the nurses just have the local knowledge on the ground on the day. (C2:2)

> I'm not sure how reliable those bleep numbers are but ... I don't even look at them now I still go back to ringing switchboard and trying to find out. (C3:6)

> ... it's very difficult to locate an orthopaedic doctor so I guess that our first port of call isn't actually the orthopaedic team, it would be the on-call medical team or ITU. (ON3:12)

> ... we're just communicating. We just talk to people a lot of the time. (ON3:19)

3.2 Discussing the cases

Once the appropriate doctors had been located to formally alert them to an AKI patient in their care, there were differences between consultants and nurses experiences due to the differing intervention pathways, but there were also similarities. Firstly, these respondents provide a general overview of their respective approaches. A consultant describes their general intervention pathway:

> I phone them up and I give them advice and make sure that they are repeating the bloods and doing all the appropriate things I think they need to do and it may be a case of just saying 'are you aware' and they say 'yes' and I say 'fine you're doing all the right things' or it may be much more detailed advice depending on the situation … (C2:5)

For outreach nurses, there were some pathway differences between the sites due to the professional judgements and discretion of the outreach team members. This did have the potential however of causing confusion among doctors who work across three sites:

> ... we look to see where the patients are ... and then we go out to the wards to see the patients and speak to the teams so we'll put a sticker in the notes alerting the team to the patient ... and we'll find out ... what's happening with the patient ... then we'll speak directly with the teams about that. And then if we feel that they need continued monitoring then we'll retain them on our list. If not, that will be our only contact with them. (ON3:7)
>
> Other people on that initial visit, even if it's basic, might still go on to do a complete full assessment ... And I think that's when then you get a differing expectation maybe from the medical teams. (ON2:10)

However, respondents found that in most cases action had already been taken:

> … by and large I think that by the time I get round to speaking to the team they're usually aware that the patient has AKI. I cannot really recall any instance, maybe one or two instances in the last year or however long since we rolled it out, that I phoned a team and they were genuinely unaware. (C2:9)
>
> ... the doctors that I've spoken to will say 'oh yes we know about the patient, we've done A B and C and we're awaiting X Y and Z' so most of the times they are already on the case and our advice isn't needed. (C1:5)

While nurses had similar experiences, they felt that the stickers were instrumental in bringing about an awareness:

> Quite honestly, I think the stickers have been quite successful – generally [the teams have] already identified that they've got acute kidney injury, they've already started all the processes on the advice sticker and we stick the sticker on the notes anyway, even though it's all happening. (ON3:7)

When it came to reactions from doctors to these interventions, respondents had mixed experiences. This respondent for example felt that consultant colleagues were supportive overall:

> I have spoken to other consultants, medical consultants in other hospitals and they say it's a good thing that someone else is keeping an eye and providing that extra layer of advice to their teams. (C1:4)

For outreach nurses, despite the sticker often being applied after the event, these respondents were keen to point out that this did not seem to interfere with interpersonal relationships with the teams:

> ... but they've identified it, they've done it all and then we've come along with our sticker! But I think there is sort of quite a... a good rapport with them ... And we just go, "Ha, ha, ha. I'm afraid it's got to go in there," because it's like an audit trail, isn't it? ... but I've *never* felt anybody was really cross about it ... (ON1:9)
>
> Not ever had a negative response from anybody. (ON2:14)
>
> ... we're quite good at... at rapport ... There's sometimes a bit of a competitive spirit as well. They go, "I've done it already!" (ON3:15)

For other respondents, the general experience of doctors' reactions varied, with some respondents perceiving some indifference due to the fact that action had already been taken:

> … it's a mixture of positive and indifferent but not negative. I've not had anyone getting irritated, cross, abusive or obviously lacking in gratitude. Indifferences maybe one third and people actually sort of sounding quite positive's probably two thirds and that is irrespective of the sort of level if you like, of the person I'm speaking to … (C2:5)

> … they've got you know other priorities they are busy ... they just give you the information and if you say something to them they will just note it down but I don't think they're hugely interested. (C3:5)

Another respondent highlighted that there could sometimes be an issue with understanding the urgency of the situation for the patient:

> ... sometimes you'll get a registrar who'll say 'well I'm in clinic I'll deal with it later' and you say 'no you can't' ... and yeah, so occasionally perhaps there's a perception issue as to the significance of the problem, it's how you handle that … (C4:10)

As intimated previously, some of the respondents did notice a difference between the teams in the Trust in how the patients were dealt with:

> ... medical teams usually have it under control, it's the surgical teams that have the challenges ... (C6:5)
>
> ... often I find that the ward manager knows far more about what's going on with Mrs Bloggs than the surgical junior doctors ... (C5:10)
>
> ... you are dependent ... on one on-call doctor at a junior level who specialises in people with broken or damaged bones who then have - this is a slightly sweeping statement that I'm going to make, - the inability to do anything about anything that's not to do with an injured bone! It's just like, "That's not my job." (ON3:12)

This respondent had a sympathetic opinion regarding these differences:

> ... I am aware that in many instances ... the surgeons are less aware but they're surgeons ... physicians should be looking after these patients ... surgeons should get on with the job they're best at ... they're not particularly concerned with post-op ... (C6:3)

It was of interest though that many of the consultants recognised the potentially intrusive nature of the alert system and were empathetic about how the phone calls could be received:

> I feel very guilty about troubling them … the post-take ward round is probably the most stressful point in the week when your workload is at its highest. And to then have somebody bugging you about a patient you already know has got AKI to tell you they've got AKI, I feel slightly guilty about to be perfectly honest … they are remarkably restrained I think. (C2:7)

> If I had a patient coming in under my care and a doctor phoned me up asking me basic questions, I would probably get a bit upset but that's me, every doctor is different. (C1:6)
>
> ... it's sort of stepping on professional toes a little bit ... there is perhaps sometimes a worry that we almost take a bit of a holier than thou attitude ...you know, somebody coming in and, not even invited ... and saying 'well you've got this wrong and this needs to happen', it could be perceived as you know a little bit arrogant or a bit rude. Not the intention at all. (C4:2)

3.3 Awareness of the alert system

One of the factors that influenced the response by the teams was the extent to which they were aware of the alert system. Some felt that this was an enduring problem due to working patterns, especially among junior doctors:

> The juniors ... haven't had a clue about them at all but once you get to registrar level and above they're very receptive to it ... (ON4:14)
>
> … even now I think a lot of them are basically not certain why we're ringing them … it happens, because there are so many clinicians all over and surgeons, and physicians and nurses, junior doctors. I don't think everybody knows about it. (C3:2)
>
> ... teams are changing all the time. Junior doctors change every year ... you just get one group used to the system then a new group arrives with no knowledge, no training in dealing with patients with AKI ... so it's a challenge. (C6:11)

This respondent highlighted the importance of communication skills:

> Sometimes they'll go 'ugh, no!' and don't know about the system ... they're not fully aware that they might get a phone call, so how you introduce yourself in the first instance I think sets a tone of the rest of your discussion … (C4:10)

For others, there had been more problems at the beginning of the project:

> I think in the early days people were surprised that someone else was aware of that clinical issue … sometimes if you rang you'd end up speaking to the ward … and then they would say 'sorry, who are you? And what system is

this?' … So it's almost like sometimes I felt I was a bogus caller … then eventually, eventually now it's old hat they generally are aware. (C1:4)

Well, we did some work early on in getting round to tell people about the system ... getting buy-in ... (C6:3)

3.4 Summary

There were similarities between how consultants and nurses approached 'alerting' and discussing cases with the relevant medical teams, however for outreach nurses, the extent of professional involvement in this varied between the hospital sites which could cause confusion among doctors. The difficulties respondents had in tracking down the appropriate junior doctor manifested themselves as a major problem and it was clearly frustrating and costly in time. Respondents highlighted the many intricate instances of how communication can fail to connect them to the right person in a timely manner. This included failures with how bleeps are managed, the complexity of junior doctors working patterns, how their responsibilities are organised, the instability of medical teams, and how the movement of patients is monitored. All respondents had developed strategies to cope with this frustration, which mainly entailed phoning the nursing staff on the wards, who they felt had more immediate knowledge of who to contact, and maintaining good channels of communication.

In the face of these difficulties with contact, the general experience of the respondents was that when the appropriate doctor was located and cases were discussed, most found that teams were already aware and were dealing with the situation. Outreach nurses noted the success of the stickers in bringing about awareness. Some respondents felt a degree of discomfort with ringing colleagues uninvited for little justification, noting that responses sometimes inferred disinterest. But on the whole, responses were not negative and there was a recognition of the importance of interpersonal communication skills. It appeared that there were differences between specialties; some respondents seemed not only to have greater difficulties accessing surgical and orthopaedic teams than physicians, but surgical teams were by and large less aware of their AKI patient and how to action the alert.

When it came to colleague's awareness of the alert system, respondents were mixed in their responses. Some felt uncertain that there was full understanding of why they were being contacted. The shifting nature of junior doctors' employment explained some of this. Others felt that there were problems at the outset but that there was now generally a good understanding.

4 Monitoring cases

While the function of the alert system is to ensure that AKI patients are identified, accountable clinicians informed and that appropriate interventions have or will be actioned, respondents were asked whether they undertook any monitoring or follow-up of cases. The two sections here focus on differing views of whether they felt they should follow up or not, and the extent to which respondents felt that advice was acted upon.

4.1 To follow up or not to follow up?

The responses were varied; these first quotes from consultants for example describe experiences where respondents were particularly concerned about inappropriate management and took action:

> … we had one last week where I felt very strongly that the patient had been inappropriately managed … my colleague went and saw the patient, you know, absolutely agreed that this was an avoidable situation that really they should have been more aware of the risks and the fact that the patient already was developing AKI … (C2:6/7)
>
> ... there are a couple of cases where I've been really, really worried about somebody ... then I will actually follow it up and look at it the next day and the next day to make sure that actually they're getting better ... (C5:10)
>
> … probably once every six or nine months then you know I feel actually this hasn't been appropriately managed and there needs to be a bit of follow through for this. (C2:6)

As intimated in earlier sections, outreach nurses' involvement varied across sites according to the condition of the patient and professional judgement:

... in my workload ... they either get a sticker and we'd never ever promise to do anything more than one visit, or they are a documented Outreach patient, so they'll have a full assessment. (ON1:10)

... if they've already identified AKI then... then that's it and we don't really necessarily go back. (ON3:11)

... you'll find people that are more complex, that have got a lot of other ongoing problems, that have got maybe multiple potential causes of their AKI that are very sick ... you keep on the Outreach list because they're sick, not necessarily just because they've got an AKI. (ON2:9/10)

These consultants however felt that the teams should be accountable following the alert communication:

I really don't see the need for further monitoring, once it's handed over then it's the responsibility of that team ... (C6:5)

I think really the ball should be in their court, whose patient it is, that they should be just chasing up and let us know if there is progress or lack or it rather than, you know, we chasing them all the time which is happening at the moment … (C3:5)

Whether they followed up cases or not, all respondents made efforts to ensure that a communication was recorded to alert the teams to their involvement, or mechanism was in place should more advice be needed:

... following up, no ... I try to remember ... put that as a final comment you know, registrar or SHO informed, discussed blah blah blah, team aware to contact renal if they have any further concerns or issues. (C4:8)

... if I was going to carry on monitoring or seeing a patient from a trigger ... I would write something at the end of the notes along the lines of *we will continue to monitor this patient's progress* and something along those lines. (ON2:10)

… obviously the team can contact you but sometimes the team will contact the on call doctor as well or would have already done that so there is a way of, for the team to follow up those cases. (C1:3)

Many of the patients eventually came under the care of the renal team:

… a lot of them do end up on dialysis and they eventually come to our ward anyway so there is that follow up. I think out of all the cases I've done there

was one that I was particularly interested in and kept contacting the team and **...** then eventually they came over to our ward … (C1:3)

4.2 Acting on advice

There were distinct differences between the consultants and outreach nurses on this subject. For consultants, the extent to which advice was acted upon was not generally known due to work patterns, as one respondent stated:

> ... you generally aren't really aware of whether it's been carried out or not - your recommendation - because the next day you're not on call again ... On one occasion I did ring to speak to the doctors and I advised them to call me back, and they never did. And for whatever reason they probably felt that they'd finished the case effectively and they didn't need my advice, I'm assuming. (C1:4)

Related to this, a further concern was the inability of teams to make a written note of the discussions with respondents, which impacted on the audit trail and clinical decision-making process. This quote summarises consultant experiences:

> What I hadn't done until recently was actually ask them to document the discussion that had been had with them. ... There's no documentation of these discussions happening, and I suspect that's because often the discussions happen when the doctor's not in front of the notes because we're ringing them and .... catching them wherever they are. (C5:8)

For the outreach nurses, there were clear comparisons between different medical teams, with significant concerns being raised again regarding the lack of appropriate trauma and orthopaedic team responses and accountability. Some of these quotes highlight the extremes that the nurses felt they needed to go to ensure the patients are appropriately managed:

> ... the medics are really very good at dealing with the acute kidney injury. The area that we have a huge problem with ... is the trauma and orthopaedic areas ... you know, they... they will watch their patient's renal function deteriorate and then the nurses will call the Outreach team to say, "This patient's got a really big problem," and then we'll tip up and start the whole ball rolling really ... in extreme cases they've already contacted the renal

team and they completely ignore the advice. And that's really an area that needs a lot of work... (ON3:11)

We've started using words like 'life-threatening' 'this patient will die' and then... and then the next thing we do is we say, "Shall we phone [the renal team] for you? Here you are; they're on the phone." (ON2:15)

... we've highlighted it, shown the doctors the stickers in the notes and said to them, "This is actually quite serious now and this patient looks like they have a potential to deteriorate. We feel that you need to take this further," and the doctors have walked past us and carried on talking to other nurses and... and we've had to wait and wait our turn to then come back to them and say, "Did you quite understand that this is serious? Can you please listen to us?" (ON4:15)

4.3 Summary

There were differences in consultants' and outreach nurses' experiences regarding monitoring patients and acting on advice given. For consultants, monitoring or follow-up of cases was conducted on few occasions and only when patients gave cause for concern, and confidence in managing the patient was not high. Some felt quite strongly that involvement should end following the alert, as teams should take over responsibility. On-going monitoring by outreach nurses varied between the three sites and was dependent upon professional judgement and the condition of the patient.

Most consultants were not aware if advice had been acted upon, and there were some concerns regarding the documenting of the advice given. However, all agreed, including nurses, that they would ensure the availability of a contact for further advice if needed. Outreach nurses focused on challenges with trauma and orthopaedic teams and highlighted the difficulties with passing on the management responsibility of AKI patients to them.

5 Impacts on Patients and Clinical Practice

This final theme is concerned with gaining perceptions of the extent to which respondents felt that their involvement in the alert system had any effects,

beneficial or otherwise, on patient care and clinical practice, as well as cost-effectiveness.

5.1 *Making a difference to patient care*

Some respondents could point to circumstances when they could be having some positive impact on patient outcomes, and outreach nurses tended to have a firm conviction that they were essentially contributing to patient benefit:

> … for the patients. I know ... I mean I don't know how many we've seen … but I *know* that there are some that we've changed things for. (ON1:24)
>
> ... how can it not be a benefit? It has to be, doesn't it. It has to be. (ON2:25)
>
> ... most AKI is ... secondary to sepsis or dehydration, or excess diuresis, you know, so actually if you can alert the teams to it and get them to intervene early, then actually you will significantly improve outcomes. (C5:12)
>
> I think sometimes ... when we pitch up a lot of the relatives and the patients are, "Oh thank goodness somebody's going to come and do something," because they've got... they've noticed that there's something wrong and it looks as if somebody's coming to sort it out so that's a patient benefit, isn't it, from their perception. (ON3:26)

But consultants were largely sceptical about the benefits. This was mostly due to the observation that teams were either already aware or full scale intervention was not clinically appropriate:

> I question whether phoning a junior doctor team or consultant ... about a patient admitted the day before with acute kidney injury and who, they must be aware if they've looked at the blood results, has AKI, I wonder whether that actually provides any added value at all. (C2:7)
>
> ... I'd say three quarters of the patients you ring up ... they're either dying and there is nothing you can do or the team's got it in hand and they know exactly what they're doing and they're doing fine. So you know it does feel sometimes like quite a lot of work for very little benefit. (C5:11)

This respondent indicated that the lack of perceived benefits stemmed from advice not being followed:

> I think that generally speaking it doesn't improve patient care ... there was one case only where I did give advice which was the correct advice and then

> we subsequently found that the advice wasn't followed and that patient was eventually transferred here for dialysis therapy so I feel that it doesn't really add to patient management ... (C1:5)

Comments were also made that suggested the need for proper comparative research and larger samples to better estimate benefits:

> … once you've, you know, given the information and instructions, what happens it's not really followed up and whether it would have made any difference you would have to compare it with somebody who has not had that, you know, data so you have to compare it with something to know whether there is a difference or not. (C3:5)

> I think there are too few numbers of patients to really point to whether it has a benefit or not, but it's brought AKI to people's attention ... we just need to have the means to track patients ... (C6:10)

The following respondent indicated that more benefits could potentially be achieved through the outreach team who focus on patients with the earlier stages of AKI:

> I think the outreach team have been looking at going out to see people with acute kidney injury stage 2 and they've actually physically seen patients and put information in the notes ... I suspect that probably the biggest benefits will have come from that intervention, getting in there a little bit earlier and actually steering people in the right direction. (C5:12)

5.2 Impacts on clinical practice

Most respondents saw both positive and negative impacts on clinical practice. The quotes below refer to cases where intervention can be positive and serve an educational purpose:

> I think that there are certain groups in the hospital that are very poor at managing the sick patients and particularly patients with AKI ... so I think that actually, I think that's where I see that we have the benefit ... when I ring up some, one of the surgeons to say did you realise your patient has deteriorating renal function ... they usually haven't got a clue ... so it does prompt them to go and actually look and get their medical review. (C5:9/10)

> ... sometimes it's not direct intervention, it's almost preventing intervention ... you know, facilitating the team making a clinical judgement on what is or isn't appropriate for the demented ninety-seven-year-old with multiple other illnesses ... So some of them are sort of much more soft interventions about sort of management strategy rather than medical treatment ... some of its educational as well. (C4:13)

The outreach nurses specifically identified the positive and proactive contribution of the stickers, as well as the ability of their involvement to reduce unnecessary work:

> And they're actually now approaching us when we go onto the unit and say, "Can we have a sticker?" and they will have people that haven't even been identified on the database as acute kidney injury and they want stickers for those notes. (ON3:7)
>
> ... whoever's on the nightshift will go round in the early hours of the morning, we'd go into Qlikview, get the list out, go and identify these patients and their notes so that when they're being post-taked in the morning it's identified to the teams ... Which is ... certainly cutting out one ward round and potentially one day's worth of medical input. (ON2:17)

In addition, outreach nurses in particular saw the educational opportunities for themselves:

> I think for me it's been positive because I've... it's done a lot for my knowledge and maybe... maybe I see patients in a different way now. Sharing skills which is part of our job, people show interest in the stickers and you're able to tell them what you're looking for and why so they might pick things up about the drugs that you're looking at and so on. (ON1:24)

The following comment from a consultant indicates the benefits of an AKI database again to enhance educational opportunities in the Trust:

> ... the system does mean that we've now got a very good database of actually what sort of AKI we have in the Trust and where it is ... which groupings is it happening under and maybe an idea as to you know, who's doing well and who's not doing so well and to allow us to focus some education on those areas that aren't doing well. (C5:11)

Conversely, other comments related to the negative personal impact on practice brought about by the alert system:

> ... I think it adds to my busy day already when I've put you know, I can actually do other things ... (C1:6)
>
> … I'm not sure it's the best use of my time to be perfectly honest … a lot of it's an administrative task which is pretty tedious. (C2:9)

However, all respondents highlighted concerns regarding clinical responsibility for the patient and the impact of the alert system. This quote describes what this means in practice for consultants:

> I have quite a lot of concerns about ownership of the patients. So for example if a patient was admitted on my take, I would assume a hundred percent responsibility for ... acting and looking into each problem and dealing with it. And when you include a system like this I feel that number one ownership could be eroded and doctors ... could become more nonchalant and lethargic and say 'oh there is this computer system that could pick this patient up and because they have renal failure it's not my problem anymore' and I feel strongly about that. (C1:6)

As suggested earlier, outreach nurses had particular concerns about where their involvement began and ended, and how this was interpreted by some doctors:

> I think ownership of the... ownership of the alert system from my feeling is... becomes an issue. My feeling is that once you document in the notes 'Outreach', you then become the first point of contact for anything that ever goes wrong or problems ... you then become embroiled in the rest of the unfolding of the events. (ON2:6/7)
>
> ... some doctors will see the sticker and your signature and think that every day you're going to make sure their bloods are done and you're going to check the results. Other teams won't. Other teams will just manage what they do but it's very varied. (ON1:9)
>
> Even from the medical teams; "Mrs so-and-so – you've seen this person?" "I've kind of not really; I just stuck an ... alert sticker in the notes and signed it." (ON3:6)

This respondent made particular reference to the establishment of a specialist ortho-geriatric system that compounded the problem of patient accountability within certain surgical teams:

> ... part of the problem with trauma and orthopaedics is now that there is this ortho-geriatric system in place, it's almost exacerbated the problem of them now completely ignoring anything ... there's almost a mentality now that; *out of hours - oh that can wait, the ortho-geries will be on in the morning.* (ON2:15)

There were also concerns that the alert system had generally impacted on their professional roles in a negative way, reducing it to an unsatisfactory screening process induced by 'lists':

> I think the problem for us is that we have so many parts of our role and we've... we've become very much a list and screening culture, so we... we start off every morning with a list from the alert system, we have a list from the VitalPac, we have our list of patients and it feels very much as though we're trawling around the hospital to keep a lot of lists ... you obviously have to go through that process to get to people that you're going to have effective interactions with but it's beginning to feel like we are part of this list culture ... that's not very nice really. (ON3:17)

Continuing with outreach nurse perceptions of professional issues, respondents were aware that there were numerical differences in patient interactions brought about by the alert system between the three hospital sites. This was explained as an administrative problem with recording on two of the sites – numbers recorded did not in fact reflect activity in reality - and that there were fewer identified patients on the third:

> … we go and see these patients but we don't always at the end of the day sit down and put them on the system … Now, unless we keep all of that documentation we can't go back retrospectively and put it on the system so we ... we miss that time slot. So there are a lot of interactions we do on this site that we don't put on the system. (ON3:19)
>
> Probably at [site] our patient numbers are lower … And it is doable within our working hours. (ON1:19)

5.3 Perceptions of cost-effectiveness

It was generally difficult for respondents to express some perceptions of the extent to which they felt that the alert system saved money, but these quotes denote that it is certainly an aspiration:

> Well it costs £150 to dialyse a patient, and that's around £30,000 per patient per year ... so it would be nice to think it was making some impact on that ... (C6:10)

> If you're highlighting early people that have got an acute kidney injury that's then being treated and managed, it's got to save money in terms of length of stay and ongoing treatment or higher levels of treatment. (ON2:26)

> ... so do we save money? Don't know ... do we improve patient outcomes? One would hope to think so and actually you could then say well improving outcomes is going to be a cost saving in terms of if you can prevent somebody needing to go onto dialysis or needing to go up to ITU for haemo-filtration, yes you will save money, you will shorten their patient inpatient stay. (C4:14)

This respondent was however more sceptical:

> ... if somebody's already in ITU and being managed and they know about AKI I don't think that will save money just to tell them that he has AKI. (C3:7)

Other more comparative views focused on the cost of respondent time:

> I don't know how much Qlikview costs, I'm assuming it's part of the great IT budget of the hospital so in terms of everything else it's probably a small cost, but in terms of time at the moment it's quite costly on time. (C1:7)

> ... well it's highly cost effective at the moment because it's not included within any of our job plans to my knowledge, so essentially the Trust is getting this additional work for – for nothing! (C2:8)

5.4 Summary

Despite some respondents, largely outreach nurses, perceiving positive proactive, preventive and educational benefits for patient outcomes and clinical practice, some respondents were not wholly convinced of the value of the system in inducing these benefits, nor of being cost-effective. This scepticism resulted from the observation that most clinical teams already had the situation in hand,

or that intervention was not indicated. In addition, the small number of patients made impacts difficult to assess. An issue of concern centred on the potential of the alert system to divert perceived clinical responsibility of the patient away from the clinician who was actually accountable, and outreach nurses in particular felt that this aspect impacted on their professional roles. It was also revealed that discrepancies in outreach nurse system activity between the sites was largely a recording issue.

6 Recommendations for Improvement

6.1 Improving Trust-wide knowledge of the alert system

This should include a user-manual; an initial comprehensive and wide exposure to the new system; an on-going programme of updates; a focus on junior doctors' education; and greater visibility of the stickers.

> maybe a user's guide ... you know, an idiot's guide how to quickly get to the reporting page ... (C1:2)
>
> ... perhaps if they would have maybe sat down with everybody at the beginning and explained how the system works and what to do and how to go through the system. (C1:1)
>
> I think that it would have probably been advisable to have made it more obvious, more visible to other staff in the trust ... you'd have to kind of redo that every time you induced a new load of junior doctors across multiple sites, I'm not sure that would be practical so maybe some, you know some pre rollout announcements and so on ... (C2:2)
>
> I think [junior doctors] need to be made aware of that but that will have to be a very extensive education programme, because it's across three sites and it includes all specialities surgical, medical and the juniors change as well. (C6:4)
>
> I have to say the stickers are good. I do think the stickers need to be a bit more in your face, though, because I sometimes put them in the notes and think *mmmm, do you know what; I'd just like something a bit more out there*. (ON2:23)

6.2 Improving the technology

6.2.1 Aligning the data systems and technology

This should include improving the accessibility of clinical data sources within the alert system and its speed; providing up-to-date clinical information; improving how NHS numbers are accessed; and developing a divert directly to the clinician responsible; and having an accessible electronic form to improve reporting.

> ... well it'd be really nice if it was all in one place, that would be amazing, but you know, it's a new project and I think … you might want the Ferrari but having the Ford Fiesta is a start! (C4:5)
>
> ... if it's incorporated into the VitalPac system where you know you are highlighting patients with acute kidney injury and you can just with the click of a button look at their observations and then the historic blood results and then what has been ordered and what is awaited and it's live data, that would be ... helpful. (C1:6)
>
> ... if the system was actually – represented what, you know was real time, then ... it would save you quite a lot of time ... (C5.6)
>
> ... there should be facility to copy and paste for example the NHS number because that's how it identifies it on the monitoring form but you can't do that so you have to write it down first and then put it in there. (C3:3)
>
> ... in an ideal world there should ...some sort of link system whereby the alerts can be sent ... directly to the teams looking after that patient that says, "Your patient, Mr Smith, is an AKI 2. Deal with it please." ... if we need to be contacted for our input then we're there, however it's kind of cutting out the middle man in a sense. (ON2:17)
>
> ... doctors don't record the discussion in the notes, so there's no evidence that it existed or how it was acted on ... so it would be good to have an electronic form that could be universally accessed ... (C6:5)
>
> From a reporting point of view, we wanted to know last year how many patients we'd seen on the system ... so I guess for us it would be nice if we could have an easy to pull reporting system. (ON3:23)

6.2.2 Establishing clinical ownership of the patient and responsiveness.

This should include greater organisational accountability for tracking the whereabouts of junior doctors; developing a 'response' alert; improving pathways to clinical responsibility for patient management; and creating a clearer understanding of the role of outreach nurses, as well as reassessing their function in the alert system.

> I suspect the nursing staff on the ground probably know amongst themselves who the right person will be but that knowledge has to be translated up the corporate structure so that actually, the corporation, the organisation knows exactly how individual patients are mapped onto the junior teams. (C2:3)
>
> ….to have an alert that links to advice and then to have an escalation system whereby …. we can see where alerts hadn't been responded to …. I think that would be you know a huge advantage. (C2:9)
>
> doctors ... could become more nonchalant and lethargic and say 'oh there is this computer system that could pick this patient up and because they have renal failure it's not my problem anymore' (C1:6)

... the difficulties are that we're... we're acting as screening people ... I'm not sure that that couldn't be screened by somebody else and then we could be alerted to the fact that they need us. (ON3:6)

Appendix 7: Variables available in the risk modelling and their definitions

Table 44: Hospital Episode Database variable definitions

Data Entry	Calculated Variable	Variable Description
NHS number	Not used in analysis	Identifier used to link patient data – removed following data linkage
Trust Unique Episode Number	Not used in analysis	Identifier used following anonymisation
Gender	Gender	Gender of the patient. Coded as: 1 = Male 2 = Female
Age on Admission	Age on Admission	Age of the patient on admission to hospital
Spell Type	Spell Type	Type of patient admission. Coded as: DC = Daycase EL = Elective NEL = Non-elective
Admission Date and Time	Admissions in Last 12 Months	Using admission date the number of admissions in the last 12 months for this patient is calculated
Admission Date and Time	Admissions in Last 30 Days	Using admission date the number of admissions in the last 30 days for this patient is calculated
Length of Stay	Length of Stay	Number of days the patient remained in hospital as an inpatient.

Died in Hospital	Died in Hospital	Whether the patient died in this admission to hospital.
Admission Source	Increase in Care on Discharge	By comparison of admission source and discharge destination an assessment of increase in care (from home to residential or nursing care) is made.
Discharge Destination	Increase in Care on Discharge	By comparison of admission source and discharge destination an assessment of increase in care (from home to residential or nursing care) is made.
Primary Diagnosis	Primary Diagnosis Group	Individual primary diagnosis for this admission coded by ICD-10 is re-coded into ICD-10 group.
Secondary Diagnoses	Individual Co-morbidity: AIDS Any Malignancy Except Skin Chronic Heart Failure Congestive Pulmonary Disease Cerebrovascular Disease Dementia Diabetes	Up to 12 secondary diagnoses are coded per hospital episode. All previous episode (i.e. not this present episode of care) secondary diagnoses are used to define the Charlson individual co-morbidities using validated coding

	Hemiplegia of Paraplegia Hypertension Myocardial Infarction Metastatic Solid Tumour Mild Liver Disease Mod/Severe Liver Disease Peripheral Vascular Disease Peptic Ulcer Disease Renal Disease Rheumatic Disease	algorithms.
Secondary Diagnoses	Modified Charlson co-morbidity Score	Up to 12 secondary diagnoses are coded per hospital episode. All previous episode (i.e. not this present episode of care) secondary diagnoses are used to define the modified Charlson co-morbidity score using a validated algorithm.
Outpatient Appointment Date	Outpatient Attendances in Last 12 Months	Using outpatient appointment date and the outcome field (ATT = attended) the number of outpatient attendances in the last 12 months for this patient is calculated.
Renal Modality	Not used in analysis	This data variable was linked from the Renal

		system at EKHUFT, using NHS number, in order to remove patients on renal replacement therapy (RRT) from the analysis.

Table 45: Pathology Database variable definitions

Data Entry	Calculated Variable	Variable Description
ALT (Alanine Transaminase)	ALT – 12 Month Average	Average of all ALT results in the 12 months prior to hospital admission.
ALT (Alanine Transaminase)	ALT – Most Recent Result	Most recent ALT result within the last 30 days prior to hospital admission.
ALT (Alanine Transaminase)	ALT – Admission Result	Peak ALT result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
ALT (Alanine Transaminase)	ALT – 72 Hour Peak	Peak ALT result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
AMY (Amylase)	AMY – 12 Month Average	Average of all AMY results in the 12 months prior to hospital

		admission.
AMY (Amylase)	AMY – Most Recent Result	Most recent AMY result within the last 30 days prior to hospital admission.
AMY (Amylase)	AMY – Admission Result	Peak AMY result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
AMY (Amylase)	AMY – 72 Hour Peak	Peak AMY result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
BNP (Brain Natriuretic Peptide)	BNP – 12 Month Average	Average of all BNP results in the 12 months prior to hospital admission.
BNP (Brain Natriuretic Peptide)	BNP – Most Recent Result	Most recent BNP result within the last 30 days prior to hospital admission.
Ca (Corrected Calcium)	Ca – 12 Month Average	Average of all Ca results in the 12 months prior to hospital admission.
Ca (Corrected Calcium)	Ca – Most Recent Result	Most recent Ca result within the last 30 days prior to hospital

		admission.
Ca (Corrected Calcium)	Ca – Admission Result	Peak Ca result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Ca (Corrected Calcium)	Ca – 72 Hour Peak	Peak Ca result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
CRP (C-Reactive Protein)	CRP – 12 Month Average	Average of all CRP results in the 12 months prior to hospital admission.
CRP (C-Reactive Protein)	CRP – Most Recent Result	Most recent CRP result within the last 30 days prior to hospital admission.
CRP (C-Reactive Protein)	CRP – Admission Result	Peak CRP result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
CRP (C-Reactive Protein)	CRP – 72 Hour Peak	Peak CRP result within 12 hours post admission to 72 hours post admission time (taken

		from ‘Admission Date and Time’ data entry in Table 44).
Hb (Haemoglobin)	Hb – 12 Month Average	Average of all Hb results in the 12 months prior to hospital admission.
Hb (Haemoglobin)	Hb – Most Recent Result	Most recent Hb result within the last 30 days prior to hospital admission.
Hb (Haemoglobin)	Hb – Admission Result	Peak Hb result within 12 hours pre to 12 hours post admission time (taken from ‘Admission Date and Time’ data entry in Table 44).
Hb (Haemoglobin)	Hb – 72 Hour Peak	Peak Hb result within 12 hours post admission to 72 hours post admission time (taken from ‘Admission Date and Time’ data entry in Table 44).
HBA1CHbA1c (Glycated Haemoglobin)	HBA1C – 12 Month Average	Average of all HBA1C results in the 12 months prior to hospital admission.
HBA1CHbA1c (Glycated Haemoglobin)	HBA1C – Most Recent Result	Most recent HBA1C result within the last 30 days prior to hospital admission.
K (Potassium)	K – 12 Month Average	Average of all K results in

		the 12 months prior to hospital admission.
K (Potassium)	K – Most Recent Result	Most recent K result within the last 30 days prior to hospital admission.
K (Potassium)	K – Admission Result	Peak K result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
K (Potassium)	K – 72 Hour Peak	Peak K result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Mg (Magnesium)	Mg – 12 Month Average	Average of all Mg results in the 12 months prior to hospital admission.
Mg (Magnesium)	Mg – Most Recent Result	Most recent Mg result within the last 30 days prior to hospital admission.
Mg (Magnesium)	Mg – Admission Result	Peak Mg result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).

Mg (Magnesium)	Mg – 72 Hour Peak	Peak Mg result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Na (Sodium)	Na – 12 Month Average	Average of all Na results in the 12 months prior to hospital admission.
Na (Sodium)	Na – Most Recent Result	Most recent Na result within the last 30 days prior to hospital admission.
Na (Sodium)	Na – Admission Result	Peak Na result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Na (Sodium)	Na – 72 Hour Peak	Peak Na result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
PLT (Platelets)	PLT – 12 Month Average	Average of all PLT results in the 12 months prior to hospital admission.
PLT (Platelets)	PLT – Most Recent Result	Most recent PLT result within the last 30 days

		prior to hospital admission.
PLT (Platelets)	PLT – Admission Result	Peak PLT result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
PLT (Platelets)	PLT – 72 Hour Peak	Peak PLT result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
WBC (White Blood Cells)	WBC – 12 Month Average	Average of all WBC results in the 12 months prior to hospital admission.
WBC (White Blood Cells)	WBC – Most Recent Result	Most recent WBC result within the last 30 days prior to hospital admission.
WBC (White Blood Cells)	WBC – Admission Result	Peak WBC result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
WBC (White Blood Cells)	WBC – 72 Hour Peak	Peak WBC result within 12 hours post admission to 72 hours post

		admission time (taken from 'Admission Date and Time' data entry in Table 44).
CK (Creatine Kinase)	CK – Most Recent Result	Most recent CK result within the last 30 days prior to hospital admission.
CK (Creatine Kinase)	CK – Admission Result	Peak CK result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
CK (Creatine Kinase)	CK – 72 Hour Peak	Peak CK result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
BC (Blood Culture)	BC – 2 Weeks Taken	Binary BC taken (Y/N) within the 2 weeks prior to hospital admission.
BC (Blood Culture)	BC – 2 Weeks Significant Growth	Binary BC reported with significant growth (Y/N) within the 2 weeks prior to hospital admission.
BC (Blood Culture)	BC – 24 Hours Taken	Binary BC taken (Y/N) within 12 hours pre to 12 hours post admission time (taken from

		'Admission Date and Time' data entry in Table 44).
BC (Blood Culture)	BC – 72 Hours Taken	Binary BC taken (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
BC (Blood Culture)	BC – 72 Hours Significant Growth	Binary BC reported with significant growth (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
FAE (Faeces Culture)	FAE – 2 Weeks Taken	Binary FAE taken (Y/N) within the 2 weeks prior to hospital admission.
FAE (Faeces Culture)	FAE – 2 Weeks Significant Growth	Binary FAE reported with significant growth (Y/N) within the 2 weeks prior to hospital admission.
FAE (Faeces Culture)	FAE – 24 Hours Taken	Binary FAE taken (Y/N) within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table

		44).
FAE (Faeces Culture)	FAE – 72 Hours Taken	Binary FAE taken (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
FAE (Faeces Culture)	FAE – 72 Hours Significant Growth	Binary FAE reported with significant growth (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
MSU OR CSU (Mid-Stream Specimen Urine or Catheter Specimen Urine)	MSU OR CSU – 2 Weeks Taken	Binary MSU OR CSU taken (Y/N) within the 2 weeks prior to hospital admission.
MSU OR CSU (Mid-Stream Specimen Urine or Catheter Specimen Urine)	MSU OR CSU – 2 Weeks Significant Growth	Binary MSU OR CSU reported with significant growth (Y/N) within the 2 weeks prior to hospital admission.
MSU OR CSU (Mid-Stream Specimen Urine or Catheter Specimen Urine)	MSU OR CSU – 24 Hours Taken	Binary MSU OR CSU taken (Y/N) within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).

MSU OR CSU (Mid-Stream Specimen Urine or Catheter Specimen Urine)	MSU OR CSU – 72 Hours Taken	Binary MSU OR CSU taken (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
MSU OR CSU (Mid-Stream Specimen Urine or Catheter Specimen Urine)	MSU OR CSU – 72 Hours Significant Growth	Binary MSU OR CSU reported with significant growth (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
SPU (Sputum Culture)	SPU – 2 Weeks Taken	Binary SPU taken (Y/N) within the 2 weeks prior to hospital admission.
SPU (Sputum Culture)	SPU – 2 Weeks Significant Growth	Binary SPU reported with significant growth (Y/N) within the 2 weeks prior to hospital admission.
SPU (Sputum Culture)	SPU – 24 Hours Taken	Binary SPU taken (Y/N) within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
SPU (Sputum Culture)	SPU – 72 Hours Taken	Binary SPU taken (Y/N) within 12 hours pre to 72

		hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
SPU (Sputum Culture)	SPU – 72 Hours Significant Growth	Binary SPU reported with significant growth (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
SAP (Swab, Aspirate, Pus Culture)	SAP – 2 Weeks Taken	Binary SAP taken (Y/N) within the 2 weeks prior to hospital admission.
SAP (Swab, Aspirate, Pus Culture)	SAP – 2 Weeks Significant Growth	Binary SAP reported with significant growth (Y/N) within the 2 weeks prior to hospital admission.
SAP (Swab, Aspirate, Pus Culture)	SAP – 24 Hours Taken	Binary SAP taken (Y/N) within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
SAP (Swab, Aspirate, Pus Culture)	SAP – 72 Hours Taken	Binary SAP taken (Y/N) within 12 hours pre to 72 hours post admission time (taken from

		'Admission Date and Time' data entry in Table 44).
SAP (Swab, Aspirate, Pus Culture)	SAP – 72 Hours Significant Growth	Binary SAP reported with significant growth (Y/N) within 12 hours pre to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Cr (Creatinine)	Baseline Cr	Lowest Cr in the 12 months prior to hospital admission (not including the 2 weeks prior to admission).
Cr (Creatinine)	Baseline eGFR	eGFR calculated using the MDRD equation, based on the Baseline Cr.
Cr (Creatinine)	Baseline CKD Stage	CKD Stage based on the Baseline eGFR.
Cr (Creatinine)	Pre-Admission Cr	Peak Cr in the 2 weeks prior to hospital admission (from 12 hours pre admission up to 2 weeks (taken from 'Admission Date and Time' data entry in Table 44)).
Cr (Creatinine)	Pre-Admission AKI Stage	AKI Stage based on the Pre-Admission Cr.
Cr (Creatinine)	Admission Cr	Peak Creatinine within

		12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Cr (Creatinine)	Admission AKI Stage	AKI Stage based on the Admission Cr.
Cr (Creatinine)	72 Hour Peak Cr	Peak Cr within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Cr (Creatinine)	72 Hour AKI Stage	AKI Stage based on the 72 Hour Peak Cr.
Trop (Troponin)	Trop – 12 Month Test Count	Number of Trop tests performed in the 12 months prior to hospital admission.
Trop (Troponin)	Trop – 12 Month Positive Count	Number of Trop tests classed as positive for myocardial infarction in the 12 months prior to hospital admission.
Trop (Troponin)	Trop – Admission Result	Peak Trop result within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Trop (Troponin)	Trop – Admission Result	Binary Trop tested (Y/N)

	Tested	within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Trop (Troponin)	Trop – Admission Result Positive	Binary Trop result positive for myocardial infarction (Y/N) within 12 hours pre to 12 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Trop (Troponin)	Trop – 72 Hour Peak	Peak Trop result within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Trop (Troponin)	Trop – 72 Hour Result Tested	Binary Trop tested (Y/N) within 12 hours post admission to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Trop (Troponin)	Trop – 72 Hour Peak Result Positive	Binary Trop result positive for myocardial infarction (Y/N) within 12 hours post admission

		to 72 hours post admission time (taken from 'Admission Date and Time' data entry in Table 44).
Albumin Creatinine Ratio (ACR) Protein Creatinine Ratio (PCR)	Prot – 12 Month Test Count	Number of Prot tests performed in the 12 months prior to hospital admission (taken from 'Admission Date and Time' data entry in Table 44).
Albumin Creatinine Ratio (ACR) Protein Creatinine Ratio (PCR)	Prot – 12 Month Worst Stage	Worst Prot stage (either ACR or PCR, as defined by KDIGO (Table 48)) in the 12 months prior to hospital admission (taken from 'Admission Date and Time' data entry in Table 44).

Table 46: Electronic Discharge Notification Database variable definitions

Data Entry	**Calculated Variable**	**Variable Description**
Medication Name	Angiotensin Converting Enzyme Inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) Count	From medication name field of last discharge summary for that patient and cross reference with lookup table of medication names and parent groups, calculation of number of this class of medication.

Medication Name	Non-Steroidal Anti-Inflammatory Count	From medication name field of last discharge summary for that patient and cross reference with lookup table of medication names and parent groups, calculation of number of this class of medication.
Medication Name	Diuretic Count	From medication name field of last discharge summary for that patient and cross reference with lookup table of medication names and parent groups, calculation of number of this class of medication.
Medication Name	Total Number of Medications	Count of number of entries in the medication name field.

Table 47: Operation Database variable definitions

Data Entry	**Calculated Variable**	**Variable Description**
Operation Date and Time	24 Hour Operation Performed	Binary (Y/N) operation performed in the first 24 hours of admission (taken from 'Admission Date and Time' data entry in Table 44).
Operation Score	24 Hour Maximum Operation Score	Maximum operation score in the first 24

	(1 (least severe) to 5 (most severe))	hours of admission (taken from 'Admission Date and Time' data entry in Table 44).

Table 48: Proteinuria Classification (KDIGO) [83]

Measure	**Categories**		
	Normal to mildly increased (1)	**Moderately increased (2)**	**Severely increased (3)**
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	negative to trace	trace to +	+ or greater

Table 49: Operative Severity Score Classification

OPCS Sub-Section Code	**OPCS Sub-Section Description**	**Operative Severity Score**
#	Blank or Unknown Code	
A32	Other decompression of cranial nerve	2
A33	Neuro-stimulation of cranial nerve	1
A36	Other operations on cranial nerve	2

A39	Repair of dura	4
A40	Drainage of extradural space	4
A41	Drainage of subdural space	4
A47	Other destruction of spinal cord	4
A48	Other operations on spinal cord	4
A52	Therapeutic epidural injection	1
A53	Drainage of spinal canal	1
A54	Therapeutic spinal puncture	1
A55	Diagnostic spinal puncture	1
A57	Operations on spinal nerve root	3
A59	Excision of peripheral nerve	1
A60	Destruction of peripheral nerve	1
A61	Extirpation of lesion of peripheral nerve	1
A62	Microsurgical repair of peripheral nerve	1
A64	Other repair of peripheral nerve	1
A65	Release of entrapment of peripheral nerve at wrist	1
A66	Release of entrapment of peripheral nerve at ankle	1
A67	Release of entrapment of peripheral nerve at other site	1
A68	Other release of peripheral nerve	1
A69	Revision of release of peripheral nerve	1
A70	Neuro-stimulation of peripheral nerve	1
A73	Other operations on peripheral nerve	1
A75	Excision of sympathetic nerve	2
A76	Chemical destruction of sympathetic	1

	nerve	
A77	Cryotherapy to sympathetic nerve	1
A78	Radiofrequency controlled thermal destruction of sympathetic nerve	1
A79	Other destruction of sympathetic nerve	2
A81	Other operations on sympathetic nerve	2
A83	Electroconvulsive therapy	2
A84	Neurophysiological operations	2
B08	Excision of thyroid gland	3
B09	Operations on aberrant thyroid tissue	2
B10	Operations on thyroglossal tissue	2
B12	Other operations on thyroid gland	2
B14	Excision of parathyroid gland	2
B16	Other operations on parathyroid gland	2
B22	Excision of adrenal gland	4
B27	Total excision of breast	3
B28	Other excision of breast	2
B29	Reconstruction of breast	2
B30	Prosthesis for breast	2
B32	Biopsy of breast	1
B33	Incision of breast	1
B34	Operations on duct of breast	1
B35	Operations on nipple	1
B36	Reconstruction of nipple and areola	1
B37	Other operations on breast	2
C01	Excision of eye	3
C02	Extirpation of lesion of orbit	2
C03	Insertion of prosthesis of eye	2

C04	Attention to prosthesis of eye	1
C05	Plastic repair of orbit	2
C06	Incision of orbit	2
C08	Other operations on orbit	2
C09	Replacement of canthal tendon	2
C10	Operations on eyebrow	1
C11	Operations on canthus	1
C12	Extirpation of lesion of eyelid	1
C13	Excision of redundant skin of eyelid	1
C14	Reconstruction of eyelid	1
C15	Correction of deformity of eyelid	1
C16	Other plastic repair of eyelid	1
C17	Other repair of eyelid	1
C18	Correction of ptosis of eyelid	1
C19	Incision of eyelid	1
C20	Protective suture of eyelid	1
C22	Other operations on eyelid	1
C24	Operations on lacrimal gland	1
C25	Connection between lacrimal apparatus and nose	1
C26	Other operations on lacrimal sac	1
C27	Operations on nasolacrimal duct	1
C29	Other operations on lacrimal apparatus	1
C31	Combined operations on muscles of eye	2
C32	Recession of muscle of eye	2
C33	Resection of muscle of eye	2
C35	Other adjustment to muscle of eye	2
C37	Other operations on muscle of eye	2
C39	Extirpation of lesion of conjunctiva	1
C40	Repair of conjunctiva	1

C43	Other operations on conjunctiva	1
C44	Other plastic operations on cornea	1
C45	Extirpation of lesion of cornea	1
C46	Plastic operations on cornea	1
C47	Closure of cornea	1
C48	Removal of foreign body from cornea	1
C49	Incision of cornea	1
C51	Other operations on cornea	2
C53	Extirpation of lesion of sclera	1
C54	Buckling operations for attachment of retina	2
C55	Incision of sclera	2
C57	Other operations on sclera	2
C59	Excision of iris	2
C60	Filtering operations on iris	1
C61	Other operations on trabecular meshwork of eye	1
C62	Incision of iris	1
C64	Other operations on iris	1
C65	Operations following glaucoma surgery	2
C66	Extirpation of ciliary body	2
C69	Other operations on anterior chamber of eye	2
C71	Extracapsular extraction of lens	2
C72	Intracapsular extraction of lens	2
C73	Incision of capsule of lens	2
C74	Other extraction of lens	2
C75	Prosthesis of lens	2
C77	Other operations on lens	2
C79	Operations on vitreous body	2

C80	Operations on retinal membrane	2
C81	Photocoagulation of retina for detachment	1
C82	Destruction of lesion of retina	1
C84	Other operations on retina	2
C85	Fixation of retina	2
C86	Other operations on eye	2
C89	Operations on posterior segment of eye	2
C90	Local anaesthetics for ophthalmology procedures	1
D01	Excision of external ear	1
D02	Extirpation of lesion of external ear	1
D03	Plastic operations on external ear	1
D04	Drainage of external ear	1
D06	Other operations on external ear	1
D07	Clearance of external auditory canal	1
D08	Other operations on external auditory canal	1
D10	Exenteration of mastoid air cells	2
D12	Other operations on mastoid	2
D13	Attachment of bone anchored hearing prosthesis	2
D14	Repair of eardrum	2
D15	Drainage of middle ear	1
D16	Reconstruction of ossicular chain	2
D17	Other operations on ossicle of ear	2
D19	Extirpation of lesion of middle ear	2
D20	Other operations on middle ear	2
D23	Operations on inner ear	2
D26	Operations on vestibular apparatus	2
D28	Other operations on ear	2

E01	Excision of nose	2
E02	Plastic operations on nose	1
E03	Operations on septum of nose	1
E04	Operations on turbinate of nose	1
E05	Surgical arrest of bleeding from internal nose	1
E06	Packing of cavity of nose	1
E07	Other plastic operations on nose	1
E08	Other operations on internal nose	1
E09	Operations on external nose	1
E10	Other operations on nose	1
E12	Operations on maxillary antrum using sublabial approach	3
E13	Other operations on maxillary antrum	2
E14	Operations on frontal sinus	2
E15	Operations on sphenoid sinus	2
E16	Other operations on frontal sinus	2
E17	Operations on unspecified nasal sinus	2
E19	Excision of pharynx	4
E20	Operations on adenoid	2
E21	Repair of pharynx	3
E23	Other open operations on pharynx	3
E24	Therapeutic endoscopic operations on pharynx	2
E25	Diagnostic endoscopic examination of pharynx	1
E27	Other operations on pharynx	3
E28	Operations on cricopharyngeus muscle	2
E29	Excision of larynx	4

E30	Open extirpation of lesion of larynx	3
E31	Reconstruction of larynx	3
E33	Other open operations on larynx	3
E34	Microtherapeutic endoscopic operations on larynx	2
E35	Other therapeutic endoscopic operations on larynx	2
E36	Diagnostic endoscopic examination of larynx	1
E38	Other operations on larynx	3
E39	Partial excision of trachea	3
E40	Plastic operations on trachea	3
E41	Open placement of prosthesis in trachea	3
E42	Exteriorisation of trachea	3
E43	Other open operations on trachea	3
E48	Therapeutic fibreoptic endoscopic operations on lower respiratory tract	1
E49	Diagnostic fibreoptic endoscopic examination of lower respiratory tract	1
E50	Therapeutic endoscopic operations on lower respiratory tract using rigid bronchoscope	1
E51	Diagnostic endoscopic examination of lower respiratory tract using rigid bronchoscope	1
E52	Other operations on bronchus	4
E59	Other operations on lung	4
E85	Ventilation support	3
E95	Tuberculosis support	1

F01	Partial excision of lip	1
F02	Extirpation of lesion of lip	1
F03	Correction of deformity of lip	1
F04	Other reconstruction of lip	1
F05	Other repair of lip	1
F06	Other operations on lip	1
F08	Implantation of tooth	1
F09	Surgical removal of tooth	2
F10	Simple extraction of tooth	1
F12	Surgery on apex of tooth	1
F13	Restoration of tooth	1
F14	Orthodontic operations	1
F15	Other orthodontic operations	1
F16	Other operations on tooth	1
F17	Operations on teeth using dental crown or bridge	1
F18	Excision of dental lesion of jaw	2
F20	Operations on gingiva	2
F22	Excision of tongue	4
F23	Extirpation of lesion of tongue	2
F24	Incision of tongue	2
F26	Other operations on tongue	3
F28	Extirpation of lesion of palate	2
F29	Correction of deformity of palate	3
F30	Other repair of palate	2
F32	Other operations on palate	2
F34	Excision of tonsil	2
F36	Other operations on tonsil	2
F38	Extirpation of lesion of other part of mouth	2
F39	Reconstruction of other part of mouth	3

F40	Other repair of other part of mouth	3
F42	Other operations on mouth	2
F43	Other examinations of mouth	1
F44	Excision of salivary gland	2
F45	Extirpation of lesion of salivary gland	1
F46	Incision of salivary gland	1
F48	Other operations on salivary gland	1
F51	Open extraction of calculus from salivary duct	1
F53	Other open operations on salivary duct	1
F56	Manipulative removal of calculus from salivary duct	1
F58	Other operations on salivary duct	1
F63	Insertion of dental prosthesis	1
G02	Total excision of oesophagus	4
G07	Repair of oesophagus	4
G09	Incision of oesophagus	3
G10	Open operations on varices of oesophagus	4
G13	Other open operations on oesophagus	4
G14	Fibreoptic endoscopic extirpation of lesion of oesophagus	2
G15	Other therapeutic fibreoptic endoscopic operations on oesophagus	2
G16	Diagnostic fibreoptic endoscopic examination of oesophagus	1
G17	Endoscopic extirpation of lesion of oesophagus using rigid	2

	oesophagoscope	
G18	Other therapeutic endoscopic operations on oesophagus using rigid oesophagoscope	2
G19	Diagnostic endoscopic examination of oesophagus using rigid oesophagoscope	2
G21	Other operations on oesophagus	3
G23	Repair of diaphragmatic hernia	3
G24	Antireflux operations	3
G25	Revision of antireflux operations	3
G27	Total excision of stomach	4
G28	Partial excision of stomach	4
G29	Open extirpation of lesion of stomach	3
G31	Connection of stomach to duodenum	3
G32	Connection of stomach to transposed jejunum	4
G33	Other connection of stomach to jejunum	3
G34	Artificial opening into stomach	2
G35	Operations on ulcer of stomach	3
G36	Other repair of stomach	3
G38	Other open operations on stomach	3
G40	Incision of pylorus	3
G42	Other fibreoptic endoscopic extirpation of lesion of upper gastrointestinal tract	2
G43	Fibreoptic endoscopic extirpation of lesion of upper gastrointestinal tract	2
G44	Other therapeutic fibreoptic	2

	endoscopic operations on upper gastrointestinal tract	
G45	Diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract	1
G46	Therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract	2
G47	Intubation of stomach	2
G49	Excision of duodenum	4
G51	Bypass of duodenum	3
G52	Operations on ulcer of duodenum	3
G53	Other open operations on duodenum	3
G55	Diagnostic endoscopic examination of duodenum	1
G57	Other operations on duodenum	3
G58	Excision of jejunum	4
G59	Extirpation of lesion of jejunum	3
G60	Artificial opening into jejunum	2
G61	Bypass of jejunum	3
G63	Other open operations on jejunum	3
G64	Therapeutic endoscopic operations on jejunum	2
G67	Other operations on jejunum	3
G69	Excision of ileum	4
G71	Bypass of ileum	3
G72	Other connection of ileum	3
G73	Attention to connection of ileum	3
G74	Creation of artificial opening into ileum	3
G75	Attention to artificial opening into	2

	ileum	
G76	Intra-abdominal manipulation of ileum	3
G78	Other open operations on ileum	3
G80	Diagnostic endoscopic examination of ileum	1
G82	Other operations on ileum	3
H01	Emergency excision of appendix	2
H02	Other excision of appendix	2
H03	Other operations on appendix	2
H04	Total excision of colon and rectum	4
H05	Total excision of colon	4
H06	Extended excision of right hemicolon	4
H07	Other excision of right hemicolon	4
H08	Excision of transverse colon	4
H09	Excision of left hemicolon	4
H10	Excision of sigmoid colon	4
H11	Other excision of colon	4
H12	Extirpation of lesion of colon	3
H13	Bypass of colon	3
H14	Exteriorisation of caecum	3
H15	Other exteriorisation of colon	3
H16	Incision of colon	3
H17	Intra-abdominal manipulation of colon	3
H18	Open endoscopic operations on colon	2
H19	Other open operations on colon	3
H20	Endoscopic extirpation of lesion of colon	2
H21	Other therapeutic endoscopic	2

	operations on colon	
H22	Diagnostic endoscopic examination of colon	1
H24	Other therapeutic endoscopic operations on lower bowel using fibreoptic sigmoidoscope	2
H25	Diagnostic endoscopic examination of lower bowel using fibreoptic sigmoidoscope	1
H26	Endoscopic extirpation of lesion of sigmoid colon using rigid sigmoidoscope	2
H27	Other therapeutic endoscopic operations on sigmoid colon using rigid sigmoidoscope	2
H28	Diagnostic endoscopic examination of sigmoid colon using rigid sigmoidoscope	1
H29	Subtotal excision of colon	4
H30	Other operations on colon	3
H33	Excision of rectum	4
H34	Open extirpation of lesion of rectum	3
H35	Fixation of rectum for prolapse	3
H36	Other abdominal operations for prolapse of rectum	3
H40	Operations on rectum through anal sphincter	2
H41	Other operations on rectum through anus	2
H42	Perineal operations for prolapse of rectum	2
H44	Manipulation of rectum	2

H46	Other operations on rectum	3
H47	Excision of anus	4
H48	Excision of lesion of anus	3
H49	Destruction of lesion of anus	3
H50	Repair of anus	2
H51	Excision of haemorrhoid	2
H52	Destruction of haemorrhoid	2
H53	Other operations on haemorrhoid	2
H54	Dilation of anal sphincter	2
H55	Other operations on perianal region	2
H56	Other operations on anus	2
H57	Other operations on the anal sphincter to control continence	2
H58	Drainage through perineal region	2
H59	Excision of pilonidal sinus	2
H60	Other operations on pilonidal sinus	2
H62	Other operations on bowel	3
H68	Diagnostic endoscopic examination of enteric pouch using colonoscope	1
H69	Diagnostic endoscopic examination of enteric pouch using fibreoptic sigmoidoscope	1
H70	Diagnostic endoscopic examination of enteric pouch using rigid sigmoidoscope	1
J02	Partial excision of liver	4
J04	Repair of liver	4
J08	Therapeutic endoscopic operations on liver using laparoscope	3
J09	Diagnostic endoscopic examination of liver using laparoscope	2
J10	Transluminal operations on blood	2

	vessel of liver	
J12	Other therapeutic percutaneous operations on liver	2
J13	Diagnostic percutaneous operations on liver	2
J14	Other puncture of liver	2
J15	Transluminal insertion of prosthesis into blood vessel of liver	2
J18	Excision of gall bladder	3
J20	Repair of gall bladder	3
J21	Incision of gall bladder	2
J23	Other open operations on gall bladder	3
J24	Therapeutic percutaneous operations on gall bladder	2
J32	Repair of bile duct	3
J33	Incision of bile duct	3
J34	Plastic repair of sphincter of Oddi using duodenal approach	3
J37	Other open operations on bile duct	3
J40	Endoscopic retrograde placement of prosthesis in bile duct	2
J41	Other therapeutic endoscopic retrograde operations on bile duct	2
J42	Therapeutic endoscopic retrograde operations on pancreatic duct	2
J43	Diagnostic endoscopic retrograde examination of bile duct and pancreatic duct	2
J47	Therapeutic percutaneous insertion of prosthesis into bile duct	2
J48	Other therapeutic percutaneous	2

	operations on bile duct	
J50	Percutaneous examination of bile duct	2
J52	Other operations on bile duct	2
J57	Other partial excision of pancreas	4
J60	Other open operations on pancreatic duct	3
J67	Diagnostic percutaneous operations on pancreas	2
J68	Other operations on pancreas	3
J69	Total excision of spleen	4
J72	Other operations on spleen	4
J76	Therapeutic percutaneous operations on bile duct	2
K14	Other open operations on septum of heart	4
K47	Repair of coronary artery	4
K49	Transluminal balloon angioplasty of coronary artery	2
K60	Cardiac pacemaker system introduced through vein	2
K61	Other cardiac pacemaker system	2
K62	Therapeutic transluminal operations on heart	2
L12	Other open operations on pulmonary artery	4
L13	Transluminal operations on pulmonary artery	3
L16	Extra-anatomic bypass of aorta	4
L18	Emergency replacement of aneurysmal segment of aorta	4
L19	Other replacement of aneurysmal	4

	segment of aorta	
L20	Other emergency bypass of segment of aorta	4
L21	Other bypass of segment of aorta	4
L22	Attention to prosthesis of aorta	4
L25	Other open operations on aorta	4
L26	Transluminal operations on aorta	3
L27	Transluminal insertion of stent graft for aneurysmal segment of aorta	3
L28	Transluminal operations on aneurysmal segment of aorta	3
L29	Reconstruction of carotid artery	3
L30	Other open operations on carotid artery	3
L31	Transluminal operations on carotid artery	3
L37	Reconstruction of subclavian artery	4
L38	Other open operations on subclavian artery	4
L39	Transluminal operations on subclavian artery	3
L41	Reconstruction of renal artery	4
L42	Other open operations on renal artery	4
L43	Transluminal operations on renal artery	2
L45	Reconstruction of other visceral branch of abdominal aorta	4
L47	Transluminal operations on other visceral branch of abdominal aorta	2
L48	Emergency replacement of aneurysmal iliac artery	4

L49	Other replacement of aneurysmal iliac artery	4
L50	Other emergency bypass of iliac artery	4
L51	Other bypass of iliac artery	4
L52	Reconstruction of iliac artery	4
L53	Other open operations on iliac artery	4
L54	Transluminal operations on iliac artery	2
L56	Emergency replacement of aneurysmal femoral artery	4
L57	Other replacement of aneurysmal femoral artery	4
L58	Other emergency bypass of femoral artery	4
L59	Other bypass of femoral artery	4
L60	Reconstruction of femoral artery	4
L62	Other open operations on femoral artery	4
L63	Transluminal operations on femoral artery	2
L65	Revision of reconstruction of artery	4
L66	Other therapeutic transluminal operations on artery	3
L67	Excision of other artery	4
L68	Repair of other artery	4
L70	Other open operations on other artery	4
L71	Therapeutic transluminal operations on other artery	3
L72	Diagnostic transluminal operations	3

	on other artery	
L74	Arteriovenous shunt	2
L75	Other arteriovenous operations	3
L76	Endovascular placement of stent	3
L79	Other operations on vena cava	4
L84	Combined operations on varicose vein of leg	2
L85	Ligation of varicose vein of leg	2
L86	Injection into varicose vein of leg	2
L87	Other operations on varicose vein of leg	2
L88	Transluminal operations on varicose vein of leg	2
L89	Other endovascular placement of stent	2
L90	Open removal of thrombus from vein	2
L91	Other vein related operations	2
L92	Unblocking of access catheter	1
L93	Other open operations on vein	2
L94	Therapeutic transluminal operations on vein	2
L95	Diagnostic transluminal operations on vein	2
L96	Percutaneous removal of thrombus from vein	2
L97	Other operations on blood vessel	3
L98	Operations on microvascular vessel	2
L99	Other therapeutic transluminal operations on vein	2
M02	Total excision of kidney	4
M03	Partial excision of kidney	4

M04	Open extirpation of lesion of kidney	3
M05	Open repair of kidney	3
M06	Incision of kidney	3
M09	Therapeutic endoscopic operations on calculus of kidney	2
M10	Other therapeutic endoscopic operations on kidney	2
M11	Diagnostic endoscopic examination of kidney	2
M13	Percutaneous puncture of kidney	2
M14	Extracorporeal fragmentation of calculus of kidney	2
M15	Operations on kidney along nephrostomy tube track	2
M16	Other operations on kidney	3
M18	Excision of ureter	4
M19	Urinary diversion	3
M20	Replantation of ureter	3
M21	Other connection of ureter	3
M22	Repair of ureter	3
M23	Incision of ureter	3
M25	Other open operations on ureter	3
M26	Therapeutic nephroscopic operations on ureter	2
M27	Therapeutic ureteroscopic operations on ureter	2
M28	Other endoscopic removal of calculus from ureter	2
M29	Other therapeutic endoscopic operations on ureter	2
M30	Diagnostic endoscopic examination of ureter	2

M31	Extracorporeal fragmentation of calculus of ureter	2
M32	Operations on ureteric orifice	3
M33	Percutaneous ureteric stent procedures	2
M34	Total excision of bladder	3
M35	Partial excision of bladder	3
M37	Other repair of bladder	3
M38	Open drainage of bladder	3
M39	Other open operations on contents of bladder	3
M41	Other open operations on bladder	3
M42	Endoscopic extirpation of lesion of bladder	2
M43	Endoscopic operations to increase capacity of bladder	2
M44	Other therapeutic endoscopic operations on bladder	2
M45	Diagnostic endoscopic examination of bladder	1
M47	Urethral catheterisation of bladder	1
M48	Operations on bladder	3
M49	Other operations on bladder	3
M52	Abdominal operations to support outlet of female bladder	3
M53	Vaginal operations to support outlet of female bladder	3
M56	Therapeutic endoscopic operations on outlet of female bladder	3
M58	Other operations on outlet of female bladder	3
M61	Open excision of prostate	3

M65	Endoscopic resection of outlet of male bladder	3
M66	Other therapeutic endoscopic operations on outlet of male bladder	3
M67	Other therapeutic endoscopic operations on prostate	3
M68	Endoscopic insertion of prosthesis into prostate	2
M70	Other operations on outlet of male bladder	3
M71	Other operations on prostate	3
M72	Excision of urethra	3
M73	Repair of urethra	3
M75	Other open operations on urethra	3
M76	Therapeutic endoscopic operations on urethra	2
M77	Diagnostic endoscopic examination of urethra	1
M79	Other operations on urethra	2
M81	Operations on urethral orifice	2
M83	Other operations on urinary tract	3
M85	Diagnostic endoscopic examination of urinary diversion	1
N01	Extirpation of scrotum	2
N03	Other operations on scrotum	2
N05	Bilateral excision of testes	2
N06	Other excision of testis	2
N07	Extirpation of lesion of testis	2
N08	Bilateral placement of testes in scrotum	2
N09	Other placement of testis in scrotum	2
N10	Prosthesis of testis	2

N11	Operations on hydrocele sac	1
N13	Other operations on testis	2
N15	Operations on epididymis	1
N17	Excision of vas deferens	1
N19	Operations on varicocele	1
N20	Other operations on spermatic cord	1
N22	Operations on seminal vesicle	1
N24	Operations on male perineum	2
N26	Amputation of penis	2
N27	Extirpation of lesion of penis	2
N28	Plastic operations on penis	2
N30	Operations on prepuce	1
N32	Other operations on penis	2
O02	Transluminal balloon assisted coil embolisation of aneurysm of artery	2
O03	Transluminal stent assisted coil embolisation of aneurysm of artery	2
O05	Operations on dural arteriovenous fistula	4
O06	Hybrid prosthetic replacement of shoulder joint using cemented humeral component	3
O07	Hybrid prosthetic replacement of shoulder joint using cemented glenoid component	3
O08	Hybrid prosthetic replacement of shoulder joint using cement	3
O11	Other upper digestive tract	2
O12	Branch of external carotid artery	3
O14	Other lymph node	2
O15	Operations on blood vessel	2
O17	Secondary closed reduction of	3

	fracture of bone and internal fixation	
O18	Hybrid prosthetic replacement of knee joint using cement	4
O19	Other therapeutic endoscopic operations on other joint structure	2
O20	Endovascular placement of stent graft	3
O21	Total prosthetic replacement of elbow joint using cement	4
O22	Total prosthetic replacement of elbow joint not using cement	4
O23	Total prosthetic replacement of elbow joint	4
O24	Prosthetic replacement of head of radius using cement	3
O25	Prosthetic replacement of head of radius not using cement	3
O26	Other prosthetic replacement of head of radius	3
O27	Other stabilising operations on joint	3
O29	Excision of bone	3
P01	Operations on clitoris	1
P03	Operations on Bartholin gland	1
P05	Excision of vulva	3
P06	Extirpation of lesion of vulva	2
P09	Other operations on vulva	2
P11	Extirpation of lesion of female perineum	2
P13	Other operations on female perineum	2
P14	Incision of introitus of vagina	2

P15	Other operations on introitus of vagina	2
P17	Excision of vagina	3
P18	Other obliteration of vagina	3
P19	Excision of band of vagina	2
P20	Extirpation of lesion of vagina	2
P21	Plastic operations on vagina	2
P22	Repair of prolapse of vagina and amputation of cervix uteri	3
P23	Other repair of prolapse of vagina	3
P24	Repair of vault of vagina	3
P25	Other repair of vagina	3
P26	Introduction of supporting pessary into vagina	1
P27	Exploration of vagina	1
P29	Other operations on vagina	2
P31	Operations on pouch of Douglas	3
P32	Other plastic operations on vagina	2
Q01	Excision of cervix uteri	2
Q02	Destruction of lesion of cervix uteri	2
Q03	Biopsy of cervix uteri	2
Q05	Other operations on cervix uteri	2
Q07	Abdominal excision of uterus	3
Q08	Vaginal excision of uterus	3
Q09	Other open operations on uterus	3
Q10	Curettage of uterus	2
Q11	Other evacuation of contents of uterus	2
Q12	Intrauterine contraceptive device	1
Q14	Introduction of abortifacient into uterine cavity	2
Q15	Introduction of other substance into	2

	uterine cavity	
Q16	Other vaginal operations on uterus	2
Q17	Therapeutic endoscopic operations on uterus	2
Q18	Diagnostic endoscopic examination of uterus	2
Q20	Other operations on uterus	2
Q22	Bilateral excision of adnexa of uterus	3
Q23	Unilateral excision of adnexa of uterus	3
Q24	Other excision of adnexa of uterus	3
Q25	Partial excision of fallopian tube	3
Q27	Open bilateral occlusion of fallopian tubes	2
Q28	Other open occlusion of fallopian tube	2
Q29	Open reversal of female sterilisation	3
Q30	Other repair of fallopian tube	3
Q31	Incision of fallopian tube	2
Q32	Operations on fimbria	2
Q34	Other open operations on fallopian tube	3
Q35	Endoscopic bilateral occlusion of fallopian tubes	2
Q38	Other therapeutic endoscopic operations on fallopian tube	2
Q39	Diagnostic endoscopic examination of fallopian tube	2
Q41	Other operations on fallopian tube	2
Q43	Partial excision of ovary	3
Q45	Repair of ovary	3

Q47	Other open operations on ovary	3
Q48	Oocyte recovery	2
Q49	Therapeutic endoscopic operations on ovary	2
Q50	Diagnostic endoscopic examination of ovary	2
Q51	Other operations on ovary	3
Q55	Other examination of female genital tract	1
R01	Therapeutic endoscopic operations on fetus	2
R05	Diagnostic percutaneous examination of fetus	2
R10	Other operations on amniotic cavity	2
R12	Operations on gravid uterus	2
R14	Surgical induction of labour	2
R17	Elective caesarean delivery	3
R18	Other caesarean delivery	3
R19	Breech extraction delivery	2
R20	Other breech delivery	2
R21	Forceps cephalic delivery	2
R22	Vacuum delivery	2
R23	Cephalic vaginal delivery with abnormal presentation of head at delivery without instrument	2
R24	Normal delivery	2
R27	Other operations to facilitate delivery	2
R28	Instrumental removal of products of conception from delivered uterus	2
R29	Manual removal of products of conception from delivered uterus	2

R30	Other operations on delivered uterus	2
R32	Repair of obstetric laceration	2
R37	Non-routine obstetric scan for fetal observations	1
R43	Ultrasound monitoring	1
S01	Plastic excision of skin of head or neck	1
S02	Plastic excision of skin of abdominal wall	1
S03	Plastic excision of skin of other site	1
S04	Other excision of skin	1
S05	Microscopically controlled excision of lesion of skin	1
S06	Other excision of lesion of skin	1
S08	Curettage of lesion of skin	1
S09	Photodestruction of lesion of skin	1
S10	Other destruction of lesion of skin of head or neck	1
S11	Other destruction of lesion of skin of other site	1
S13	Punch biopsy of skin	1
S14	Shave biopsy of skin	1
S15	Other biopsy of skin	1
S17	Distant flap of skin and muscle	3
S18	Distant flap of skin and fascia	3
S19	Distant pedicle flap of skin	3
S20	Other distant flap of skin	3
S21	Hair bearing flap of skin	3
S23	Flap operations to relax contracture of skin	3
S24	Local flap of skin and muscle	3

S25	Local flap of skin and fascia	3
S26	Local subcutaneous pedicle flap of skin	3
S27	Other local flap of skin	3
S30	Other operations on flap of skin to head or neck	3
S31	Other operations on flap of skin to other site	3
S33	Hair bearing graft of skin to scalp	2
S35	Split autograft of skin	2
S36	Other autograft of skin	2
S37	Other graft of skin	2
S38	Graft of mucosa	2
S39	Graft of other tissue to skin	2
S40	Other closure of skin	1
S41	Suture of skin of head or neck	1
S42	Suture of skin of other site	1
S43	Removal of repair material from skin	1
S44	Removal of other inorganic substance from skin	1
S45	Removal of other substance from skin	1
S47	Opening of skin	1
S48	Insertion of skin expander into subcutaneous tissue	1
S49	Attention to skin expander in subcutaneous tissue	1
S50	Introduction of other inert substance into subcutaneous tissue	1
S52	Introduction of Therapeutic Substance Into Subcutaneous	1

S53	Introduction of substance into skin	1
S54	Exploration of burnt skin of head or neck	1
S55	Exploration of burnt skin of other site	1
S56	Exploration of other skin of head or neck	1
S57	Exploration of other skin of other site	1
S58	Larvae therapy of skin	1
S60	Other operations on skin	1
S62	Other operations on subcutaneous tissue	1
S64	Extirpation of nail bed	1
S66	Other operations on nail bed	1
S68	Excision of nail	1
S70	Other operations on nail	1
T01	Partial excision of chest wall	4
T03	Opening of chest	4
T05	Other operations on chest wall	4
T07	Open excision of pleura	4
T08	Open drainage of pleural cavity	3
T12	Puncture of pleura	2
T16	Other repair of diaphragm	4
T19	Simple excision of inguinal hernial sac	2
T20	Primary repair of inguinal hernia	2
T21	Repair of recurrent inguinal hernia	2
T22	Primary repair of femoral hernia	2
T23	Repair of recurrent femoral hernia	2
T24	Primary repair of umbilical hernia	2
T25	Primary repair of incisional hernia	2

T26	Repair of recurrent incisional hernia	2
T27	Repair of other hernia of abdominal wall	2
T28	Other repair of anterior abdominal wall	2
T29	Operations on umbilicus	2
T30	Opening of abdomen	3
T31	Other operations on anterior abdominal wall	2
T34	Open drainage of peritoneum	3
T36	Operations on omentum	3
T37	Operations on mesentery of small intestine	3
T38	Operations on mesentery of colon	3
T39	Operations on posterior peritoneum	3
T41	Other open operations on peritoneum	3
T42	Therapeutic endoscopic operations on peritoneum	2
T43	Diagnostic endoscopic examination of peritoneum	2
T45	Image controlled operations on abdominal cavity	2
T46	Other drainage of peritoneal cavity	3
T48	Other operations on peritoneum	3
T50	Transplantation of fascia	2
T51	Excision of fascia of abdomen	2
T52	Excision of other fascia	2
T55	Release of fascia	2
T56	Other excision of other fascia	2
T57	Other operations on fascia	2
T59	Excision of ganglion	2

T60	Re-excision of ganglion	2
T62	Operations on bursa	2
T64	Transposition of tendon	2
T65	Excision of tendon	2
T67	Primary repair of tendon	2
T68	Secondary repair of tendon	2
T69	Freeing of tendon	2
T70	Adjustment to length of tendon	2
T71	Excision of sheath of tendon	2
T72	Other operations on sheath of tendon	2
T74	Other operations on tendon	2
T76	Transplantation of muscle	3
T77	Excision of muscle	2
T79	Repair of muscle	2
T80	Release of contracture of muscle	2
T81	Biopsy of muscle	2
T83	Other operations on muscle	2
T85	Block dissection of lymph nodes	2
T86	Sampling of lymph nodes	1
T87	Excision or biopsy of lymph node	1
T88	Drainage of lesion of lymph node	1
T90	Contrast radiology of lymphatic tissue	1
T91	Operations on sentinel lymph node	2
T94	Operations on branchial cleft	2
T96	Other operations on soft tissue	2
T97	Repair of recurrent umbilical hernia	2
U07	Diagnostic imaging of chest	1
U08	Diagnostic imaging of abdomen	1
U09	Diagnostic imaging of pelvis	1
U11	Diagnostic imaging of vascular	1

	system	
U16	Diagnostic imaging of hepatobiliary system	1
U20	Diagnostic echocardiography	1
U21	Diagnostic imaging procedures	1
U24	Diagnostic audiology	1
V05	Other operations on cranium	4
V06	Excision of maxilla	3
V07	Excision of bone of face	3
V08	Reduction of fracture of maxilla	2
V09	Reduction of fracture of other bone of face	2
V10	Division of bone of face	2
V11	Fixation of bone of face	2
V13	Other operations on bone of face	2
V14	Excision of mandible	3
V15	Reduction of fracture of mandible	2
V16	Division of mandible	2
V17	Fixation of mandible	2
V19	Other operations on mandible	2
V21	Other operations on temporomandibular joint	2
V22	Primary decompression operations on cervical spine	3
V24	Decompression operations on thoracic spine	3
V25	Primary decompression operations on lumbar spine	3
V26	Revisional decompression operations on lumbar spine	3
V27	Decompression operations on unspecified spine	3

V28	Insertion of lumbar interspinous process spacer	3
V29	Primary excision of cervical intervertebral disc	3
V33	Primary excision of lumbar intervertebral disc	3
V34	Revisional excision of lumbar intervertebral disc	3
V35	Excision of unspecified intervertebral disc	3
V37	Primary fusion of joint of cervical spine	3
V38	Primary fusion of other joint of spine	3
V39	Revisional fusion of joint of spine	3
V40	Stabilisation of spine	3
V41	Instrumental correction of deformity of spine	3
V44	Decompression of fracture of spine	3
V46	Fixation of fracture of spine	3
V47	Biopsy of spine	1
V48	Denervation of spinal facet joint of vertebra	2
V49	Exploration of spine	2
V50	Manipulation of spine	2
V52	Other operations on intervertebral disc	3
V54	Other operations on spine	3
V55	Levels of spine	1
V60	Primary percutaneous decompression using coblation to intervertebral disc	2

V67	Other primary decompression operations on lumbar spine	2
V68	Other revisional decompression operations on lumbar spine	2
W01	Complex reconstruction of thumb	2
W02	Other complex reconstruction of hand	2
W03	Complex reconstruction of forefoot	3
W04	Complex reconstruction of hindfoot	3
W05	Prosthetic replacement of bone	4
W06	Total excision of bone	3
W07	Excision of ectopic bone	3
W08	Other excision of bone	3
W09	Extirpation of lesion of bone	3
W10	Open surgical fracture of bone	3
W12	Angulation periarticular division of bone	2
W13	Other periarticular division of bone	2
W14	Diaphyseal division of bone	2
W15	Division of bone of foot	2
W16	Other division of bone	2
W17	Other reconstruction of bone	3
W18	Drainage of bone	2
W19	Primary open reduction of fracture of bone and intramedullary fixation	2
W20	Primary open reduction of fracture of bone and extramedullary fixation	2
W21	Primary open reduction of intra-articular fracture of bone	2
W22	Other primary open reduction of fracture of bone	2
W23	Secondary open reduction of	2

	fracture of bone	
W24	Closed reduction of fracture of bone and internal fixation	2
W25	Closed reduction of fracture of bone and external fixation	2
W26	Other closed reduction of fracture of bone	2
W27	Fixation of epiphysis	2
W28	Other internal fixation of bone	2
W29	Skeletal traction of bone	2
W30	Other external fixation of bone	2
W31	Other autograft of bone	3
W32	Other graft of bone	3
W33	Other open operations on bone	3
W35	Therapeutic puncture of bone	2
W36	Diagnostic puncture of bone	2
W37	Total prosthetic replacement of hip joint using cement	4
W38	Total prosthetic replacement of hip joint not using cement	4
W39	Other total prosthetic replacement of hip joint	4
W40	Total prosthetic replacement of knee joint using cement	4
W41	Total prosthetic replacement of knee joint not using cement	4
W42	Other total prosthetic replacement of knee joint	4
W43	Total prosthetic replacement of other joint using cement	4
W44	Total prosthetic replacement of other joint not using cement	4

W45	Other total prosthetic replacement of other joint	4
W46	Prosthetic replacement of head of femur using cement	3
W47	Prosthetic replacement of head of femur not using cement	3
W48	Other prosthetic replacement of head of femur	3
W49	Prosthetic replacement of head of humerus using cement	3
W50	Prosthetic replacement of head of humerus not using cement	3
W51	Other prosthetic replacement of head of humerus	3
W52	Prosthetic replacement of articulation of other bone using cement	3
W53	Prosthetic replacement of articulation of other bone not using cement	3
W54	Other prosthetic replacement of articulation of other bone	3
W55	Prosthetic interposition reconstruction of joint	3
W56	Other interposition reconstruction of joint	3
W57	Excision reconstruction of joint	3
W58	Other reconstruction of joint	3
W59	Fusion of joint of toe	3
W60	Fusion of other joint and extra-articular bone graft	3
W61	Fusion of other joint and other	3

	articular bone graft	
W62	Other primary fusion of other joint	3
W63	Revisional fusion of other joint	3
W64	Conversion to fusion of other joint	3
W65	Primary open reduction of traumatic dislocation of joint	2
W66	Primary closed reduction of traumatic dislocation of joint	2
W67	Secondary reduction of traumatic dislocation of joint	2
W68	Primary reduction of injury to growth plate	2
W69	Open operations on synovial membrane of joint	2
W71	Other open operations on intra-articular structure	2
W72	Prosthetic replacement of ligament	2
W74	Other reconstruction of ligament	2
W75	Other open repair of ligament	2
W76	Other operations on ligament	2
W77	Stabilising operations on joint	2
W78	Release of contracture of joint	2
W79	Soft tissue operations on joint of toe	2
W80	Debridement and irrigation of joint	2
W81	Other open operations on joint	2
W82	Therapeutic endoscopic operations on semilunar cartilage	2
W83	Therapeutic endoscopic operations on other articular cartilage	2
W84	Therapeutic endoscopic operations on other joint structure	2
W85	Therapeutic endoscopic operations	2

	on cavity of knee joint	
W86	Therapeutic endoscopic operations on cavity of other joint	2
W87	Diagnostic endoscopic examination of knee joint	2
W88	Diagnostic endoscopic examination of other joint	2
W89	Other therapeutic endoscopic operations on other articular cartilage	2
W90	Puncture of joint	2
W91	Other manipulation of joint	2
W92	Other operations on joint	2
W93	Hybrid prosthetic replacement of hip joint using cemented acetabular component	4
W94	Hybrid prosthetic replacement of hip joint using cemented femoral component	4
W95	Hybrid prosthetic replacement of hip joint using cement	4
W96	Total prosthetic replacement of shoulder joint using cement	4
W97	Total prosthetic replacement of shoulder joint not using cement	4
W98	Total prosthetic replacement of shoulder joint	4
X07	Amputation of arm	3
X08	Amputation of hand	3
X09	Amputation of leg	3
X10	Amputation of foot	3
X11	Amputation of toe	3

X12	Operations on amputation stump	3
X14	Clearance of pelvis	4
X20	Correction of congenital deformity of forearm	3
X21	Correction of congenital deformity of hand	3
X22	Correction of congenital deformity of hip	3
X23	Correction of congenital deformity of leg	3
X24	Primary correction of congenital deformity of foot	3
X25	Other correction of congenital deformity of foot	3
X27	Correction of minor congenital deformity of foot	3
X28	Intermittent infusion of therapeutic substance	1
X29	Continuous Infusion of therapeutic substance	1
X30	Injection of therapeutic substance	1
X32	Exchange blood transfusion	1
X33	Other blood transfusion	1
X35	Other intravenous injection	1
X36	Blood withdrawal	1
X37	Intramuscular injection	1
X38	Subcutaneous injection	1
X40	Compensation for renal failure	2
X41	Placement of ambulatory apparatus for compensation for renal failure	2
X42	Placement of other apparatus for compensation for renal failure	2

X45	Donation of organ	4
X46	Donation of other tissue	3
X48	Immobilisation using plaster cast	1
X49	Other external support of limb	1
X50	External resuscitation	4
X53	Extirpation of unspecified organ	4
X55	Other operations on unspecified organ	3
X56	Intubation of trachea	1
X59	Anaesthetic without surgery	1
X62	Assessment	1
Y02	Placement of prosthesis in organ NOC	2
Y03	Attention to prosthesis in organ NOC	2
Y05	Excision of organ NOC	4
Y06	Excision of lesion of organ NOC	3
Y07	Obliteration of cavity of organ NOC	3
Y08	Laser therapy to organ NOC	2
Y09	Chemical destruction of organ NOC	3
Y11	Other destruction of organ NOC	3
Y13	Other destruction of lesion of organ NOC	3
Y14	Placement of stent in organ NOC	2
Y15	Attention to stent in organ NOC	2
Y16	Connection of organ NOC	3
Y18	Release of organ NOC	2
Y20	Biopsy of organ NOC	2
Y22	Drainage of organ NOC	2
Y25	Suture of organ NOC	2
Y26	Other repair of organ NOC	3
Y27	Graft to organ NOC	3

Y29	Removal of foreign body from organ NOC	2
Y30	Incision of organ NOC	2
Y31	Exploration of organ NOC	2
Y32	Re-exploration of organ NOC	2
Y33	Puncture of organ NOC	2
Y35	Introduction of removable radioactive material into organ NOC	2
Y38	Injection of therapeutic substance into organ NOC	2
Y39	Injection of other substance into organ NOC	2
Y40	Dilation of organ NOC	2
Y41	Examination of organ NOC	2
Y42	Manipulation of organ NOC	2
Y44	Other methods of operation on organ NOC	2
Y48	Approach to spine through back	2
Y49	Approach through thoracic cavity	4
Y50	Approach through abdominal cavity	3
Y51	Approach to organ through artificial opening into gastrointestinal tract	3
Y52	Approach to organ through other opening	2
Y53	Approach to organ under image control	2
Y58	Harvest of skin for graft	2
Y59	Harvest of flap of skin and fascia	3
Y60	Other harvest of fascia	2
Y61	Harvest of flap of skin and muscle of trunk	3
Y63	Harvest of flap of muscle of trunk	3

Y65	Harvest of tendon	2
Y66	Harvest of bone	3
Y67	Harvest of other multiple tissue	3
Y69	Harvest of other tissue	2
Y70	Early operations NOC	1
Y71	Late operations NOC	1
Y74	Minimal access to thoracic cavity	3
Y75	Minimal access to abdominal cavity	2
Y76	Minimal access to other body cavity	2
Y78	Arteriotomy approach to organ under image control	2
Y80	General anaesthetic	2
Y81	Spinal anaesthetic	1
Y82	Local anaesthetic	1
Y96	In vitro fertilisation	1
Y99	Donor status	1

Appendix 8: Paper 5: National Institute for Health Research – Health Service and Delivery Research - Report - 11/2004/28

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Abstract

Development of risk models for the prediction of new or worsening acute kidney injury on or during hospital admission: a cohort and nested study

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Background: Acute kidney injury (AKI) is a common clinical problem with significant morbidity and mortality. All hospitalised patients are at risk. AKI is often preventable and reversible; however, the 2009 National Confidential Enquiry into Patient Outcome and Death [National Confidential Enquiry into Patient Outcome Death. *An Age Old Problem. A review of the Care Received by Elderly Patients Undergoing Surgery*. London: NCEPOD; 2010] highlighted systematic failings of identification and management, and recommended risk assessment of all emergency admissions [Stewart J, Findlay G, Smith N, Kelly K, Mason M. *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)*. London: National Confidential Enquiry into Patient Outcome and Death; 2009].

Objectives: To develop three predictive models to stratify the risk of (1) AKI on arrival in hospital; (2) developing AKI during admission; and (3) worsening AKI if already present; and also to (4) develop a clinical algorithm for patients admitted to hospital and explore effective methods of delivery of this information at the point of care.

Study design: Quantitative methodology (1) to formulate predictive risk models and (2) to validate the models in both our population and a second population. Qualitative methodology to plan clinical decision support system (CDSS) development and effective integration into clinical care.

Settings and participants: Quantitative analysis – the study population comprised hospital admissions to three acute hospitals of East Kent Hospitals University NHS Foundation Trust in 2011, excluding maternity and elective admissions. For validation in a second population the study included hospital admissions to Medway NHS Foundation Trust. Qualitative analysis – the sample consisted of six renal consultants (interviews) and six outreach nurses (focus group), with representation from all sites.

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ABSTRACT

Data collection: Data (comprising age, sex, comorbidities, hospital admission and outpatient history, relevant pathology tests, drug history, baseline creatinine and chronic kidney disease stage, proteinuria, operative procedures and microbiology) were collected from the hospital data warehouse and the pathology and surgical procedure databases.

Data analysis: Quantitative – both traditional and Bayesian regression methods were used. Traditional methods were performed using ordinal logistic regression with univariable analyses to inform the development of multivariable analyses. Backwards selection was used to retain only statistically significant variables in the final models. The models were validated using actual and predicted probabilities, an area under the receiver operating characteristic (AUROC) curve analysis and the Hosmer–Lemeshow test. Qualitative – content analysis was employed.

Main outcome measures: (1) a clinical pratice algorithm to guide clinical alerting and risk modeling for AKI in emergency hospital admissions; (2) identification of the key variables that are associated with the risk of AKI; (3) validated risk models for AKI in acute hospital admissions; and (4) a qualitative analysis providing guidance as to the best approach to the implementation of clinical alerting to highlight patients at risk of AKI in hospitals.

Findings: Quantitative – we have defined a clinical practice algorithm for risk assessment within the first 24 hours of hospital admission. Bayesian methodology enabled prediction of low risk but could not reliably identify high-risk patients. Traditional methods identified key variables, which predict AKI both on admission and at 72 hours post admission. Validation demonstrated an AUROC curve of 0.75 and 0.68, respectively. Predicting worsening AKI during admission was unsuccessful. Qualitative – analysis of AKI alerting gave valuable insights in terms of user friendliness, information availability, clinical communication and clinical responsibility, and has informed CDSS development.

Conclusions: This study provides valuable evidence of relationships between key variables and AKI. We have developed a clinical algorithm and risk models for risk assessment within the first 24 hours of hospital admission. However, the study has its limitations, and further analysis and testing, including continuous modelling, non-linear modelling and interaction exploration, may further refine the models. The qualitative study has highlighted the complexity regarding the implementation and delivery of alerting systems in clinical practice.

Funding: The National Institute for Health Research Health Services and Delivery Research programme.

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Appendix 9: NHS England patient safety alert and national algorithm to define AKI

Patient Safety Alert

Stage Three: Directive

Standardising the early identification of Acute Kidney Injury

9 June 2014

Alert reference number:	NHS/PSA/D/2014/010
Alert stage:	Three - Directive

National patient safety data tells us that patients are dying and suffering severe harm due to a delay in detecting Acute Kidney Injury (AKI). AKI often occurs without causing any symptoms or signs and its presence frequently goes unrecognised by patients and doctors alike.

> *"A patient with a complex physical and mental health background became unwell over a weekend. Despite persistent hypotension there was no record of fluid balance. Bloods were delayed until late Sunday night, indicating acute kidney injury. Acute kidney injury not recognised or commented on until mid way through the following day. Medications given to the patient over the weekend included drugs contraindicated in renal failure. The patient was admitted to ICU and on admission was unconscious/shocked. There were multiple systematic failures in the management of this patient including a life threatening delay in critical care of >12 hours and systems failure in the recognition of deteriorating patients."*

Acute Kidney Injury (AKI) is a sudden reduction in kidney function. Complex long term medical conditions, medication and intercurrent illness are often complicated by AKI. It is estimated that 1 in 5 emergency admissions into hospital are associated with AKI, prolonging inpatient care and contributing to 100,000 deaths in secondary care. National Confidential Enquiry into Patient Outcome and Death (NCEPOD) estimated that one quarter to one third of cases have the potential to be prevented.

A national algorithm, standardising the definition of AKI has now been agreed. This provides the ability to ensure that a timely and consistent approach to the detection and diagnosis of patients with AKI is taken across the NHS.

This algorithm has been endorsed by NHS England and it is recommended that the algorithm is implemented across the NHS. When integrated into a Laboratory Information Management System (LIMS) the algorithm will identify potential cases of AKI from laboratory data in real time and produce a test result. The laboratory system will then send the test result, using existing IT connections to patient management systems.

NHS England in partnership with the UK Renal Registry has launched a National AKI Prevention Programme which will include the development of tools and interventions. A priority for the Programme is the development and adoption of e-alert systems, based on the test result, which will proactively notify clinicians when a patient has AKI, supporting implementation of AKI NICE guidance (CG169).

Although primary care is an important focus for detection and prevention of AKI, it is anticipated that AKI results will be sent to primary care in a second phase of the programme. Meanwhile Trusts are expected to discuss with primary care representatives the management of AKI test results, particularly at times when deputizing services are providing medical cover.

Further support will be provided by the National Programme as exemplar e-alerting system are developed: www.england.nhs.uk/AKIProgramme

The AKI detection algorithm can be found at the following link: www.england.nhs.uk/aki-algorithm

Actions

Who: NHS acute trusts and foundation trusts providing pathology services

When: By 9 March 2015

1. Bring this alert to the Director of Pathology/IT with responsibility for the upgrading of LIMS systems
2. Work with local LIMS supplier to integrate AKI algorithm into LIMS system
3. Work with local LIMS supplier to ensure the test result goes to local Patient management systems and into a data message sent to a central point for national monitoring purposes
4. Communicate with appropriate primary care providers to ensure they seek advice if test results are received
5. Regularly access NHS England AKI website where additional resources and information will be provided as developed

Supporting information
For further information to support the implementation of this alert go to www.england.nhs.uk/aki-algorithm

Patient Safety | Domain 5
www.england.nhs.uk/patientsafety

Contact us: patientsafety.enquiries@nhs.net
Sign up for regular updates: www.england.nhs.uk/patientsafety

Publications Gateway Reference: 01702

Figure 74: NHS England Patient Safety Alert – Stage Three: Directive: Standardising the early identification of Acute Kidney Injury – 9th June 2014 (https://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki.pdf)

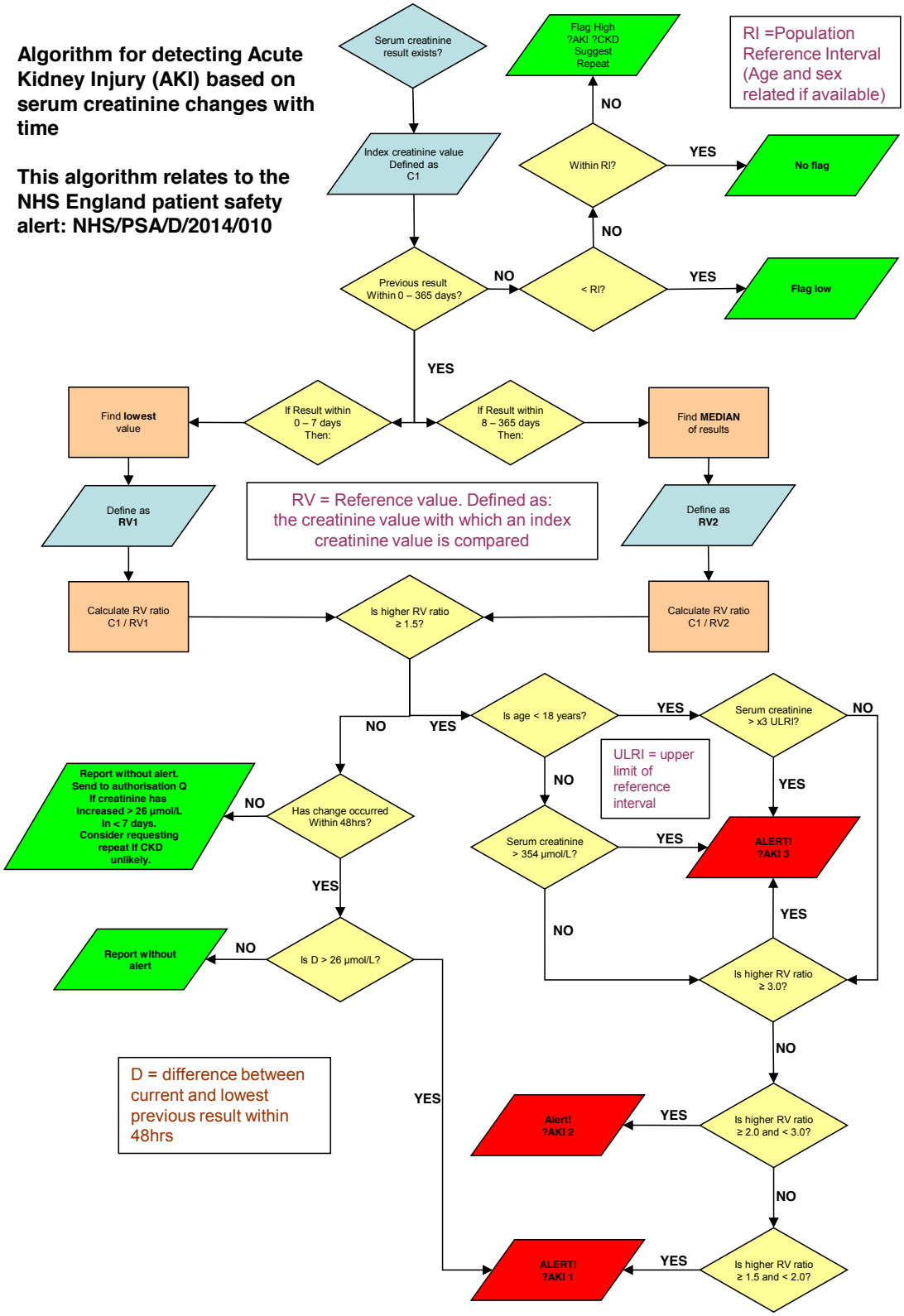

Figure 74: NHS England algorithm for detecting acute kidney injury (AKI) based on serum creatinine changes with time, (www.england.nhs.uk/aki-algorithm) [99]