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The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation

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Abstract

The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation

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Background: Acute kidney injury (AKI) is highly prevalent in hospital inpatient populations, leading to significant mortality and morbidity, reduced quality of life and high short- and long-term health-care costs for the NHS. New diagnostic tests may offer an earlier diagnosis or improved care, but evidence of benefit to patients and of value to the NHS is required before national adoption.

Objectives: To evaluate the potential for AKI in vitro diagnostic tests to enhance the NHS care of patients admitted to the intensive care unit (ICU) and identify an efficient supporting research strategy.

Data sources: We searched ClinicalTrials.gov, The Cochrane Library databases, Embase, Health Management Information Consortium, International Clinical Trials Registry Platform, MEDLINE, *meta*Register of Current Controlled Trials, PubMed and Web of Science databases from their inception dates until September 2014 (review 1), November 2015 (review 2) and July 2015 (economic model). Details of databases used for each review and coverage dates are listed in the main report.

Review methods: The AKI-Diagnostics project included horizon scanning, systematic reviewing, meta-analysis of sensitivity and specificity, appraisal of analytical validity, care pathway analysis, model-based lifetime economic evaluation from a UK NHS perspective and value of information (VOI) analysis.

Results: The horizon-scanning search identified 152 potential tests and biomarkers. Three tests, Nephrocheck® (Astute Medical, Inc., San Diego, CA, USA), NGAL and cystatin C, were subjected to detailed review. The meta-analysis was limited by variable reporting standards, study quality and heterogeneity, but sensitivity was between 0.54 and 0.92 and specificity was between 0.49 and 0.95 depending on the test. A bespoke critical appraisal framework demonstrated that analytical validity was also poorly reported in many instances. In the economic model the incremental cost-effectiveness ratios ranged from £11,476 to £19,324 per quality-adjusted life-year (QALY), with a probability of cost-effectiveness between 48% and 54% when tests were compared with current standard care.

Limitations: The major limitation in the evidence on tests was the heterogeneity between studies in the definitions of AKI and the timing of testing.

Conclusions: Diagnostic tests for AKI in the ICU offer the potential to improve patient care and add value to the NHS, but cost-effectiveness remains highly uncertain. Further research should focus on the mechanisms by which a new test might change current care processes in the ICU and the subsequent cost and QALY implications. The VOI analysis suggested that further observational research to better define the prevalence of AKI developing in the ICU would be worthwhile. A formal randomised controlled trial of biomarker use linked to a standardised AKI care pathway is necessary to provide definitive evidence on whether or not adoption of tests by the NHS would be of value.

Study registration: The systematic review within this study is registered as PROSPERO CRD42014013919.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
BNP	brain natriuretic peptide
CEA	cost-effectiveness analysis
CEAF	cost-effectiveness acceptability frontier
CI	confidence interval
CKD	chronic kidney disease
CLSI	Clinical and Laboratory Standards Institute
CONSORT	Consolidated Standards of Reporting Trials
CPB	cardiopulmonary bypass
CTIMP	Clinical Trial of an Investigational Medicinal Product
DAC	Diagnostics Advisory Committee
DEC	Diagnostic Evidence Co-operative
DOR	diagnostic odds ratio
EQ-5D	EuroQol-5 Dimensions
ESRD	end-stage renal disease
EVPI	expected value of perfect information
EVPPI	expected value of perfect parameter information
FDA	Food and Drug Administration
FN	false negative
FP	false positive
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IGFBP-7	insulin-like growth factor-binding protein 7
IL	interleukin
INB	incremental net (health) benefit
INMB	incremental net monetary benefit
IVD	in vitro diagnostic
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	kidney injury molecule-1
L-FABP	liver fatty acid-binding protein
LR–	negative likelihood ratio
LR+	positive likelihood ratio
LTHT	Leeds Teaching Hospitals NHS Trust
NAG	*N*-acetyl-beta-D-glucosaminidase
NGAL	neutrophil gelatinase-associated lipocalin
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QAMPs	Quality Assessment of Measurement Procedures
QUADAS-2	quality assessment of diagnostic accuracy studies
RCT	randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss of Kidney function and End-stage kidney disease
RR	relative risk
RRT	renal replacement therapy
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SG	standard gamble
SROC	summary receiver operating characteristic
STARD	Standards for Reporting Diagnostic Accuracy

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIMP-2	tissue inhibitor of metalloproteinases 2
TN	true negative
TNF-α	tumour necrosis factor alpha
TP	true positive
TTO	time trade-off
uL-FABP	urine liver fatty acid-binding protein
VEGF	vascular endothelial growth factor
VOI	value of information

Plain English summary

Acute kidney injury (AKI) occurs in many critically ill patients and leads to poor clinical outcomes and high mortality rates, resulting in high costs to the NHS. For these reasons it is important to identify patients who are at risk or who are developing AKI so that they can be treated earlier or more intensively to limit subsequent problems as much as possible. The diagnosis of AKI can be difficult; even with the best test that we currently have (serum creatinine) AKI may not become apparent until several days after damage to the kidneys has begun. There is currently no single test that can immediately diagnose AKI or tell us how severe it will become; however, there are several tests in development that offer this potential.

The AKI-Diagnostics project identified > 150 in-development tests. Three of these tests were subjected to detailed review. Although the quality of much of the published literature did not meet ideal standards, there was evidence that these tests can help with the early identification of AKI in the intensive care unit (ICU). All three tests have the potential to be cost-effective, although there is much uncertainty about this based on the current evidence. It is recommended that further research is carried out to better understand how common AKI is in the ICU and how a positive test result will change the way that patients are treated.

Scientific summary

Background

Acute kidney injury (AKI) is highly prevalent in hospital inpatient populations, leading to significant mortality and morbidity, reduced quality of life and high short- and long-term health-care costs for the NHS. Diagnosis currently relies on serum creatinine concentrations and anuria, which are imperfect biomarkers, leading to delayed detection after initial kidney damage. New biomarker-based in vitro diagnostics (IVDs) offer an opportunity for earlier diagnosis and improved risk stratification, enabling earlier specialist referral, targeted intervention or intensification of therapy when indicated by the test.

Candidate diagnostic tests have been commercially developed and are being marketed to clinicians and commissioners. Their evidence base is variable and there is an urgent need to develop evidence for clinical utility and cost-effectiveness to guide appropriate and suitably informed adoption within routine health services.

The development of evidence for diagnostic tests has historically been inefficient, resulting in uncertain or poor-value adoption decisions. There is a time-limited opportunity to propose an efficient research strategy for AKI diagnostics in the UK.

Aims

- To evaluate the potential for AKI IVD tests to enhance the NHS care of patients admitted to the intensive care unit (ICU)
- To identify the priorities for further research and development.

Design

The AKI-Diagnostics project included a systematic review, evidence synthesis and meta-analysis, care pathway analysis, model-based economic evaluation and value of information (VOI) analysis.

Methodological scope and outputs

- Pre-analytical, analytical and biological measurement properties.
- Clinical validity (sensitivity and specificity) for relevant outcomes identified within the care pathway.
- Clinical efficacy, clinical effectiveness and cost-effectiveness of test-directed care compared with standard care.
- Value of information analysis for research prioritisation.

Methods

The systematic review consisted of three literature searches, prospectively registered on the PROSPERO database (reference number CRD42014013919):

1. A horizon-scanning search of literature published after 2004 to identify current and future biomarkers and diagnostic tests for potential use in the identification and management of AKI in critical care.

A ranking procedure was developed to prioritise tests for further review based on the state of regulatory approvals, number of citations, combined sample size, biological mechanism and expert advice.
2. A more detailed systematic review was then undertaken of the analytical and clinical validity, clinical utility and cost-effectiveness of the highest-priority biomarkers. Two independent reviewers undertook a search of 12 databases and two trials registers in November 2015 using predefined eligibility criteria, with quality assessment carried out using the QUADAS-2 (quality assessment of diagnostic accuracy studies) tool.
3. A third literature review consisted of a series of targeted searches aimed at identifying previous relevant cost-effectiveness analyses and related research to inform the development of an economic model.

The meta-analysis of diagnostic accuracy used a bivariate model to estimate joint pooled means and variances of sensitivity and specificity for each of the diagnostic tests considered for the outcome measure of AKI KDIGO (Kidney Disease: Improving Global Outcomes). Separate meta-analyses were conducted for each diagnostic test, sample media and the two health service settings of ICU and post-cardiac surgery. Approximate estimates of the variance of sensitivity and specificity for use in the economic model were estimated using the delta method.

In the absence of a published tool, a framework for the quality assessment of measurement was developed through a process of expert consensus and review of the published literature. This was applied to a single test as proof of concept.

The economic evaluation relied on a de novo decision model constructed to determine the cost-effectiveness of the biomarkers for the early identification of AKI in the ICU from a NHS and Personal Social Services perspective. Tests were assumed to be used once on entry to the ICU. The primary analysis concerned the use of tests on an all-comer ICU population; a secondary analysis was conducted to explore the impact of the tests in a subgroup of patients in the ICU post cardiac surgery. Costs were reported in 2015 prices and effectiveness was measured in terms of quality-adjusted life-years (QALYs). All future cost and QALY outcomes were discounted at an annual rate of 3.5%.

Model parameters were estimated using individual patient clinical trial and registry data, supplemented when necessary with information from the published literature, which was identified through a series of targeted systematic literature reviews. Uncertainty around parameter estimates was characterised by assigning probability distributions to each of the uncertain parameters according to available variance data. Probabilistic sensitivity analysis was then conducted using 10,000 Monte Carlo simulations. Cost-effectiveness was assessed in terms of the incremental net (health) benefit (INB) and the incremental cost-effectiveness ratio (ICER). The cost-effectiveness threshold was taken as £20,000 per QALY unless otherwise stated.

The VOI analysis used the measures expected value of perfect information (EVPI) and expected value of perfect parameter information (EVPPI), calculated using non-parametric regression meta-modelling techniques including a generalised additive model and multivariate adaptive regression splines. Individual patient- and population-level estimates were calculated. The EVPPI was used to rank groups of model parameters as priorities for further research.

Results

Horizon-scanning search

The scoping search identified 4804 references. After screening by title/abstract, 487 potentially relevant papers remained, relating to 152 individual biomarkers. Those already used in standard care ($n = 11$, including serum creatinine) or with incomplete data related to the dimensions outlined earlier ($n = 19$) were excluded. Ten priority biomarkers/tests were shortlisted: brain natriuretic peptide (BNP), cystatin C, interleukin (IL)-6, IL-18, kidney injury molecule-1 (KIM-1), liver fatty acid-binding protein (L-FABP),

N-acetyl-beta-D-glucosaminidase (NAG), Nephrocheck® (Astute Medical, Inc., San Diego, CA, USA), neutrophil gelatinase-associated lipocalin (NGAL) and tumour necrosis factor alpha (TNF-α).

Systematic review and meta-analysis

Detailed review was undertaken for the top three ranked diagnostic tests: Nephrocheck (urine), which measures a combination of two proteins, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7); NGAL protein; and cystatin C protein. The different media of blood serum, blood plasma and urine were considered separately.

Nephrocheck

Ten studies were included in the review and three were included in the meta-analysis in the critical care setting using urine. The median age of participants in the studies was 64 years and 58% of participants were male. Using the high sensitivity cut-off value (0.3), pooled sensitivity was estimated as 0.90 [95% confidence interval (CI) 0.85 to 0.93] and pooled specificity was estimated as 0.49 (95% CI 0.46 to 0.53). No clinical efficacy, clinical utility or cost-effectiveness studies were identified. One study was included in the cardiac surgery setting using serum, with a sensitivity of 0.92 (95% CI 0.76 to 0.98) and specificity of 0.67 (95% CI 0.47 to 0.82).

Neutrophil gelatinase-associated lipocalin

Thirty-nine studies were included in the review. There was heterogeneity in the outcome definitions, assessment period and threshold used to define a positive test. Eight studies were included in the meta-analysis in the critical care setting using plasma. For plasma, the pooled sensitivity estimate was 0.72 (95% CI 0.65 to 0.79) and the pooled specificity estimate was 0.81 (95% CI 0.75 to 0.86). For serum, one study was included, with a sensitivity of 0.54 (95% CI 0.43 to 0.65) and a specificity of 0.95 (95% CI 0.88 to 0.98). For urine, six studies were included, with a pooled sensitivity of 0.70 (0.59 to 0.80) and a pooled specificity of 0.79 (95% CI 0.71 to 0.86). In the cardiac surgery setting eight studies were included for plasma, with a pooled sensitivity of 0.62 (95% CI 0.49 to 0.74) and a pooled specificity of 0.78 (95% CI 0.75 to 0.81). For serum in the cardiac surgery setting, two studies were included, with a pooled sensitivity of 0.84 (95% CI 0.43 to 0.97) and a pooled specificity of 0.87 (95% CI 0.59 to 0.97). For urine in the cardiac surgery setting, 13 studies were included, with a pooled sensitivity of 0.66 (95% CI 0.54 to 0.76) and a pooled specificity of 0.62 (95% CI 0.41 to 0.79).

Cystatin C

Seventeen studies were included in the review. There was heterogeneity in the outcome definitions, assessment period and threshold used to define a positive test. In the meta-analysis, in the critical care setting, for plasma, three studies were included, with a pooled sensitivity of 0.72 (95% CI 0.59 to 0.82) and a pooled specificity of 0.74 (95% CI 0.65 to 0.81); for serum, four studies were included, with a pooled sensitivity of 0.76 (95% CI 0.57 to 0.88) and a pooled specificity of 0.91 (95% CI 0.85 to 0.95); and, for urine, three studies were included, with a pooled sensitivity of 0.68 (95% CI 0.43 to 0.86) and a pooled specificity of 0.76 (95% CI 0.62 to 0.86). In the cardiac surgery setting there were no suitable studies for plasma; for serum, two studies were included, with a pooled sensitivity of 0.73 (95% CI 0.65 to 0.80) and a pooled specificity of 0.72 (95% CI 0.63 to 0.79); and, for urine, two studies were included, with a pooled sensitivity of 0.52 (95% CI 0.27 to 0.76) and a pooled specificity of 0.72 (95% CI 0.36 to 0.92). Estimates of 95% prediction intervals for each test, medium and setting further demonstrated the heterogeneity in the studies considered.

Quality assessment of measurement

The defining features of 'quality' with respect to measurement procedures were agreed as 'bias', 'reproducibility' and 'applicability'. Parameters associated with biological within-individual variation, biological pre-analytical factors, technical pre-analytical variation factors and analytical factors were included within the quality assessment framework.

Application of this framework within four Nephrocheck case studies identified several measurement parameters that present a high risk of irreproducibility, including a failure to exclude samples with known interferents; a lack of internal and external quality control; and a complete lack of analytical measurement verification in all studies. It also highlighted several issues that might affect the clinical applicability of test results, including freeze–thawing of samples in the absence of validation data and against the recommendations of the manufacturer, potentially biasing clinical cut-off points and overestimating precision; use of a device in an unvalidated patient population (i.e. aged < 18 years); and reporting the median value of three measurements from different laboratories. Furthermore, it identified several issues that made assessment of the risk of bias uncertain.

Economic evaluation

The economic evaluation assessed seven testing strategies: Nephrocheck, cystatin C in urine, plasma and serum and NGAL in urine, plasma and serum. Based on the mean expected cost and QALY results, lifetime incremental QALYs ranged from 0.012 (cystatin C, urine) to 0.016 (Nephrocheck) and additional costs ranged from £149 (cystatin C, urine) to £301 (Nephrocheck). The ICERs ranged from £11,476 to £13,504 per additional QALY for the cystatin C tests and from £13,372 to £13,828 for the NGAL tests and the ICER was £19,324 for Nephrocheck. For the incremental costs, all of the testing strategies had 95% CIs ranging from –£1000 to +£1400; for the incremental QALYs, all results ranged from –0.16 to +0.19 or +0.20. The overall probability that tests are cost-effective compared with standard care was 48% for Nephrocheck, 51–52% for the NGAL tests and 52–54% for the cystatin C tests (with cystatin C in serum performing the best). Raising the threshold value to £50,000 per QALY only slightly increased these probabilities.

The results of the multiway incremental comparison indicated that, in the base-case analysis, between a threshold of £11,400 and a threshold of £25,400, cystatin C (serum) has the highest probability of cost-effectiveness compared with all other tests. Above a £25,400 threshold, NGAL (serum) is expected to be the most cost-effective strategy. All other strategies are either dominated by cystatin C (serum) or, in the case of Nephrocheck, have an ICER well above £20,000 per QALY.

Similar results were observed in the post-cardiac surgery subgroup analysis. The incremental QALYs ranged from 0.007 (cystatin C, urine) to 0.012 (NGA,L serum) and additional costs ranged from £124 (cystatin C, urine) to £205 (Nephrocheck). The ICERs were £13,051–19,287 per additional QALY for the cystatin C tests, £15,337–20,435 for the NGAL tests and £18,617 for Nephrocheck, with INB values ranging from 0.000 to 0.004 QALYs. Again, there was substantial uncertainty around these results, with a 48–52% probability that the tests would be cost-effective. In the multiway incremental analysis, only NGAL (serum) remained after removal of dominated or extendedly dominated alternatives (ICER £13,051 vs. standard care).

The model results were highly sensitive to changes in key model parameters. Scenarios that led to tests becoming non-cost-effective included shortening the time horizon of the analysis, reducing the incidence of AKI in the ICU, decreasing the impact or increasing the cost of early AKI intervention, applying a mortality risk for patients with false-positive test results, applying a cost saving for patients with negative test results and increasing the mortality rate for false-negative cases and increasing the cost of Nephrocheck.

Value of information analysis

The EVPI was positive for all analyses of the three tests that were studied in detail, suggesting that the current burden of uncertainty is high and that further research into all tests and all settings may be worthwhile. Diagnostic accuracy parameters were not associated with a high EVPPI. The results of the EVPPI analysis suggested that the highest priority areas for further research include obtaining better intelligence on the current incidence of AKI in the ICU; the impact of interventions or changes in care and associated costs in response to test results; and further research on the quality of life experienced by survivors of ICU. Some of this information (e.g. the incidence and progression of AKI) may be obtainable from growing national audits. Determining the comparative impact of patient management changes resulting from different test results, however, is likely to require randomised comparisons.

Conclusions

It is clear that very large numbers of potential biomarkers and diagnostic tests have the potential to contribute to better care for patients at risk of AKI in the critical care setting. The two-stage approach taken in this study – first, horizon scanning and then prioritising biomarkers for in-depth review – proved to be a feasible and effective strategy for dealing with the volume of literature identified, which far exceeded that identified in initial scoping searches. Despite a large volume of literature covering the prioritised tests, the quality of reporting was low, leading to a significant dropout rate between review and meta-analysis. Further efforts to promote the use of reporting standards for diagnostic tests should be undertaken.

The Nephrocheck test appeared to be the best-performing test of the three tests subjected to detailed study. It has high sensitivity and moderate specificity for AKI in adult critical care settings and there was low heterogeneity between studies in the meta-analysis. The NGAL test using plasma has moderate sensitivity and high specificity, but showed greater heterogeneity between studies. Other sample types and the cystatin C test showed evidence of considerable heterogeneity between studies.

As far as we are aware, our study is the first such initiative to attempt a systematic assessment of the quality of measurement procedures used in clinical studies or trials. Our framework proved feasible and provides a foundation for further work in this area. A key finding was that the reporting of critical measurement parameters was very poor in the identified studies and this severely hindered the reviewers' ability to assess the quality of the studies. The major limitation of the meta-analysis was a lack of standardisation in the reference standard definition of AKI as an outcome.

Each of the three tests included in the economic evaluation was found to be cost-effective when compared in two-way analyses against standard care, although the absolute difference in both costs and QALYs is likely to be small. There is substantial uncertainty around these results, with the probability of cost-effectiveness being close to 50% for all tests. The VOI analysis highlighted some of the key parameters that should be the focus of further research in this area. It is apparent that observational studies that aim to better define the current clinical care pathway for patients at risk of AKI in critical care should be a priority, as should further work to understand how the care pathway might change in response to a positive test and the effectiveness of these changes in mitigating against the development of AKI. Such studies would likely be cheap to perform compared with formal randomised controlled trials that seek to directly measure the clinical benefit and observed cost-effectiveness of tests and that may not currently represent good value for research funders. It is also of note that further studies of diagnostic accuracy for the three tests would be unlikely to change the current estimates of cost-effectiveness.

Study registration

This study is registered as PROSPERO CRD42014013919.

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Chapter 1 Background and introduction

Introduction

Acute kidney injury (AKI) has been identified as an area of unmet need affecting a sizeable population, with a health burden that has the potential for significant improvement. A large number of diagnostic tests and biomarkers feature in the published literature dating back many years but, as yet, they have failed to translate into clinical practice or meaningfully benefit patients. The AKI Diagnostics project was initiated as a direct response to this problem following initial attempts to quantify the evidence base for diagnostic tests in the specific setting of critical care. Its high-level objective was to map out a strategy for further research and development that will efficiently deliver patient benefits using this technological opportunity.

The clinical problem

The relevance of AKI (also referred to as acute kidney failure) as a major problem for public health has been recently emphasised in guidance issued by the National Institute for Health and Care Excellence (NICE).[1] NICE estimates that AKI costs the UK NHS £434–620M every year (which is more than the cost of breast, lung and skin cancer combined[2]). Moreover, according to NICE, adequate care of AKI could result in 42,000 deaths being avoided every year.

Acute kidney injury occurs in 30–70% of critically ill patients and is most commonly associated with multiorgan failure secondary to hypotension and sepsis. Patients who develop AKI have worse clinical outcomes, with a mortality rate of > 50%, which, despite advances in modern medicine, has remained unchanged for the last 30 years. Patients who develop severe AKI requiring renal replacement therapy (RRT) have a further increase in their risk of death.[3]

The recognition of AKI currently relies on a rise in serum creatinine and/or a decrease in urine output, both of which are considered relatively poor biomarkers. Serum creatinine remains a non-specific marker of AKI, being a product of muscle metabolism, and does not indicate the site of the injury or distinguish between pre-renal (functional process) and intrinsic (damage process) AKI. The generation of creatinine is dependent on muscle mass and it is therefore a very poor marker of kidney function, particularly in malnourished patients or patients with liver disease. It is recognised that a person could lose 50% of their kidney function before the serum creatinine level rises above the normal range. The rise in serum creatinine is delayed in relation to the onset of the injury and the magnitude of rise does not correlate with the severity of injury. Likewise, serum creatinine levels do not correlate well with recovery of kidney function. More specific serum and urinary biomarkers of AKI are urgently needed.[4]

The need for research

More recently it has been recognised that chronic kidney disease (CKD) occurs in 40% of survivors of AKI in critical illness and results in significant morbidity and expense. It is estimated that up to 10% of patients will not recover sufficient kidney function and will remain on RRT.[5] CKD in the UK costs £1.45B per year.[6] It is therefore important to identify patients at risk or who are developing AKI to reduce the impact, ameliorate the severity of the injury and thereby reduce its short- and long-term consequences. It was reported that, in 2009–10, patients who experienced an episode of AKI in the UK stayed in hospital an average of 4.7 days longer than patients without AKI.[2] AKI represents an important patient safety issue, as recognised by NHS England,[7] and results in a significant financial burden on health-care services. There is a great potential to prevent AKI and reduce its severity and, therefore, the medical and financial burden to the NHS.

The development of better biomarkers to detect AKI would also benefit patients at risk outside of the intensive care unit (ICU) setting. Not all hospitals in the UK have renal units and the facility to deliver RRT; in these hospitals patients who develop severe AKI requiring RRT may have to be transferred to the ICU for RRT alone, which inappropriately utilises a precious NHS resource. Earlier detection of AKI with the potential to stratify prognosis would allow for prompt transfer of patients to the correct environment for their care.

Biomarker-based in vitro diagnostics (IVDs) offer an opportunity for early diagnosis, risk stratification and monitoring, enabling earlier specialist referral, targeted intervention or intensification of therapy when indicated by the test. There is some evidence that early RRT can improve outcomes from AKI, including reducing the duration of RRT, the length of the hospital stay and the rates of CKD and long-term RRT.[8] A number of pharmaceutical interventions are in late-phase development, which will increase the opportunity for targeted intervention in the coming years. Previous therapeutic interventions have been unsuccessful, in part because of the very crude approach to AKI and the failure to understand its complexity without the use of appropriate biomarkers.

The management of the majority of cases of AKI in the ICU remains supportive, with no proven pharmacological intervention for AKI secondary to hypoperfusion and sepsis. Currently, there is no robust evidence base to guide when to initiate RRT and this is determined empirically, dependent on the clinical context and utilising serum creatinine as a marker of severity of AKI. There is an ongoing research effort internationally to discover and develop biomarkers and diagnostics for AKI. The extent to which such tests can influence the clinical decisions and change the current management of patients admitted to critical care remains unknown. There is an urgent need to evaluate the extent to which AKI diagnostics have the potential to influence outcomes through a change in clinical practice. If a model-based analysis demonstrates that AKI diagnostics can potentially change practice in a way that results in more cost-effective care, there will be value in further investment in a development programme.

The sizeable waste within the historical research process has recently been highlighted.[4,9–14] Academic and commercial communities are at the start of a new era of diagnostics development for AKI. There is a time-limited opportunity to design this UK research programme efficiently and with appropriate upfront prioritisation.

Existing research

A number of different biomarkers have been investigated in small heterogeneous studies in critically ill patients with AKI, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin (IL)-18, kidney injury molecule-1 (KIM-1), liver fatty acid-binding protein (L-FABP) and, more recently, the cell cycle arrest markers insulin-like growth factor-binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinases 2 (TIMP-2).[4] More data are required from well-conducted trials to identify both improved patient outcomes and economic benefit to the NHS before their routine use can be recommended. It is unlikely that one biomarker will fit all because of the heterogeneity of causes of AKI and, therefore, a panel of biomarkers will be required. A number of biomarkers have already been commercialised as IVD test kits and are subject to active marketing campaigns, including IGFBP-7 and TIMP-2 (Nephrocheck®, Astute Medical, San Diego, CA, USA); the NGAL test (BioPorto, Hellerup, Denmark/Alpha Laboratories, Eastleigh, UK); urine NGAL (Abbott Laboratories, Chicago, IL, USA); and the Triage® NGAL Test (Alere, Waltham, MA, USA). There is therefore a real risk that these biomarkers could be adopted by NHS laboratories and clinicians prior to the development of robust supporting evidence for clinical effectiveness and cost-effectiveness.

In 2013 a diagnostic test based on the NGAL biomarker was considered by the NICE Diagnostics Advisory Committee (DAC). It concluded that more research was needed prior to adopting the test but that this was undoubtedly an area of considerable clinical need.

Adoption of diagnostic tests in the NHS

Diagnostic tests are the foundation of the new era of personalised medicine and, as such, are critical for future effective health care. The pipeline of research and development that brings new diagnostic tests to help patients within the NHS has been criticised for failing to deliver good-quality evidence-based technologies in a timely manner. It has been highlighted that progress in personalised medicine is slower than some had expected.[15] The reasons for this are likely multifactorial but may include inadequate science or insufficient economic incentives for investing in molecular diagnostics. What has recently become clear is that the methods employed in the development of evidence for new diagnostic technologies are inadequate for the task or are not used appropriately. Work is needed to develop new ways of rapidly bringing high-quality diagnostics to the front-line care of NHS patients.

The decision to reimburse a new technology on the NHS should require evidence for quality control, safety, effectiveness and cost-effectiveness; demonstration of these aspects represents the key hurdle in the process of health technology adoption. In the UK, decision-making for diagnostics may occur at a local or a national level. The gold standard process, however, is orchestrated by the NICE DAC and its methodological advisors have identified many problems and a lack of standardisation in the requirements for evidence on safety, efficacy, effectiveness and cost-effectiveness of diagnostic tests. This contrasts with the relatively well-defined evidence requirements for pharmaceuticals, which are driven by high financial stakes and a long history of safety scandals that have prompted a stepwise tightening of licensing and regulatory requirements.

The National Institute for Health Research Diagnostic Evidence Co-operatives

In response to these concerns, in 2013 the National Institute for Health Research (NIHR) in England commissioned a network of infrastructure support organisations called the Diagnostic Evidence Co-operatives (DECs). Their mission is to engage with commercial stakeholders, academic institutions and the NHS to bring high-value and high-impact diagnostic tests to patients in an efficient manner.

The two key objectives of the DECs that the AKI-Diagnostics project addressed were (1) to devise and refine methods in IVD study design, health economics and health informatics to improve and speed up the way that IVDs can be evaluated for NHS use and (2) to invite, select and prioritise specific IVD candidates across key clinical areas from partners and interested parties and help them develop and deliver appropriate evidence.

Technical background for the methodological approach

The DECs aim to promote efficient research design for new technologies within the NHS. They acknowledge that the gold standard for demonstrating clinical utility and cost-effectiveness (and accepted by NICE) is a model-based economic evaluation, informed when possible by randomised controlled trials (RCTs). For any given clinical context, modelling will therefore commence at the very start of technology evaluation, during the process that selects and prioritises technologies for inclusion within the DEC research pipeline (*Figure 1*). By introducing a model early, it is possible to characterise the potential impact of a diagnostic test on the clinical pathway, clinical decision points and expected clinical end economic outcomes. The optimal case definition threshold (cut-off point) for tests can be proposed for cost-effectiveness in addition to clinical validity alone. Models will be maintained and updated as IVD evaluation progresses, populated by meta-analysis of evidence generated both within and external to the DEC. Probabilistic modelling will be used to characterise areas of uncertainty in the evolving evidence between each phase of development, thus enabling iterative research design efficiency. Expected cost-effectiveness and value for the NHS can be established as well as commercial headroom for relevant manufacturers. It is possible to model the cost of a

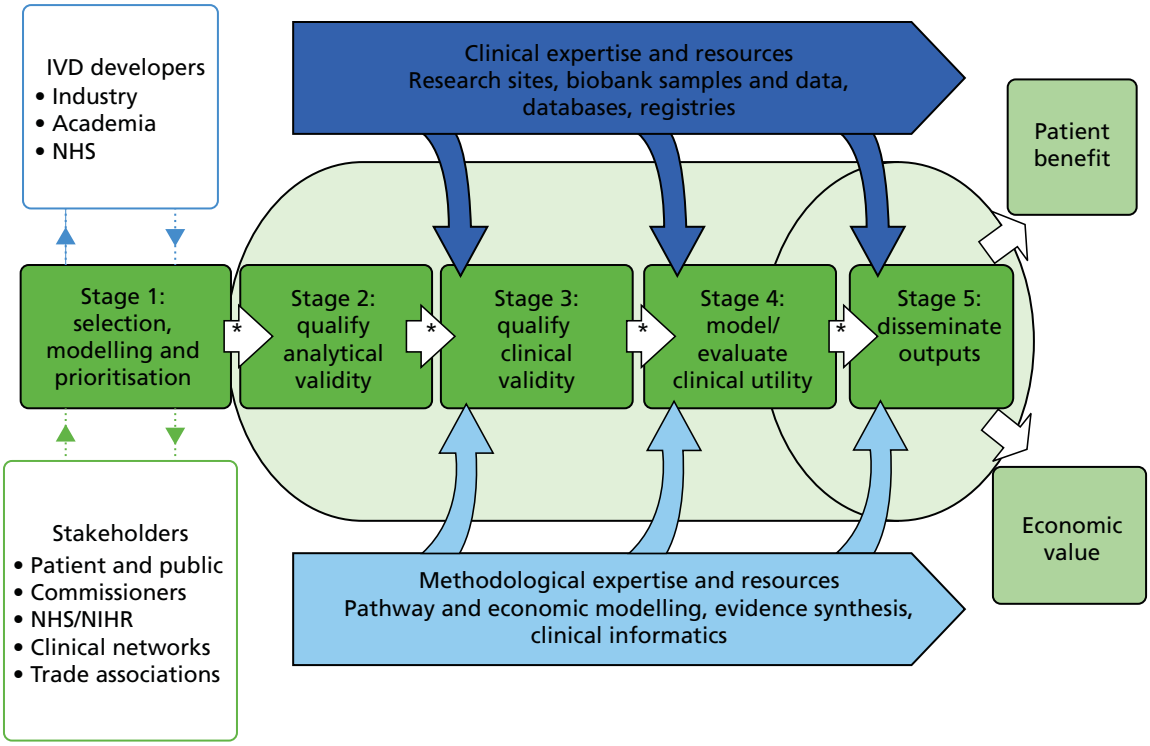

FIGURE 1 The NIHR DEC research and development pipeline. *, strategic decision-making points.

test under different commercialisation scenarios (e.g. large centralised laboratory vs. local hospital laboratory provision) and its impact on the value of alternative research activities can therefore be estimated. As an example, the trade-offs between investment in a large RCT and investment in alternative cheaper or quicker study designs can be described using the modelling process, including through the use of Bayesian decision modelling and value of information (VOI) analysis.

Project objectives

Based on the DEC methodological approach, the objectives of the AKI-Diagnostics project, focusing on critical care, were to:

- describe the care pathway followed by patients who are admitted to critical care and who are at risk of AKI, represented as a decision-analytic model
- identify, through systematic review, candidate diagnostic tests for the early detection, risk stratification or therapy personalisation of AKI
- systematically review and meta-analyse the evidence on the diagnostic properties, clinical validity and clinical utility of identified AKI diagnostic tests for AKI
- identify decision points in the care pathway that might be influenced by the diagnostic tests
- evaluate the potential clinical effectiveness and cost-effectiveness of the diagnostic tests, given their potential to change the care pathway
- characterise uncertainties in the evidence, prioritise tests for development and identify efficient research designs.

Outline of the project components

To deliver these objectives the AKI-Diagnostics project was structured into five distinct phases:

- phase 1: systematic review
- phase 2: evidence synthesis and meta-analysis
- phase 3: care pathway analysis
- phase 4: decision-analytic model
- phase 5: sensitivity analysis and VOI analysis.

Phase 1: systematic review

Phase 1 consisted of three distinct systematic literature searches and reviews. Review 1 was broad and inclusive, analogous to a horizon scan, and sought to identify candidate or in-development relevant diagnostic tests that could be used in critical care to identify AKI. Review 2 employed a focused search that identified current evidence on the analytical validity, clinical validity, clinical utility and cost-effectiveness of the prioritised tests identified in search 1. The purpose of review 3, which is reported in the health economics chapter (see *Chapter 5*), was primarily to inform the design and parameterisation of the economic model for assessing cost-effectiveness. Using a series of highly focused literature searches it aimed to identify information describing the clinical care pathway and standard care for AKI in critical care, including investigation, clinical management, interventions, health-care resource use, morbidity, mortality, quality of life and other relevant outcomes descriptors.

Phase 2: evidence synthesis and meta-analysis

Phase 2 aimed to combine the findings from phase 1 and enable summary estimation of the relevant metrics for the diagnostic properties of tests, predominantly sensitivity and specificity for relevant outcomes.

Phase 3: care pathway analysis

Phase 3 was conducted in parallel to literature search 3, using formal consultation with relevant experts and patients with the primary aim of defining standard care for patients at risk of and experiencing AKI in critical care. This was necessary as part of the economic model development process, including the identification of key decision points at which tests change the process of care, mechanisms for changing the process of care, relationships and downstream knock-on effects that may be influenced by tests and key surrogate end points. In addition to expert consultation and information obtained from literature search 3, recent UK clinical trial data sets and UK registration study data sets were identified and analysed to inform the model structure and parameters.

Phase 4: decision-analytic model

Phase 4 consisted of the construction, parameterisation and analysis of a health economic decision model based on the care pathway developed in phase 3. The model was initially designed to calculate expected costs and quality-adjusted life-years (QALYs) for the current AKI care pathway. AKI diagnostic tests were then incorporated into the model at key decision points, as indicated by the current evidence and recommendations from the specialist advisory group. Divergence in the clinical pathway consequent on test results was modelled based on the diagnostic properties and decision impact of the tests.

Phase 5: sensitivity analysis and value of information analysis

Phase 5 consisted of a series of sensitivity analyses undertaken to explore the impact of parameter and structural uncertainties on the expected cost-effectiveness of each test. In addition, VOI analysis was undertaken in an attempt to quantify the value of further publicly funded research into diagnostic tests. VOI analysis is a method based on Bayesian decision theory that can be used to characterise the burden of uncertainty on a NHS reimbursement decision-maker or commissioner.[16,17] The results were presented to guide a future research programme in this area, as needed prior to adoption of any new tests by the NHS.

Patient and public engagement in the study

Both the study research team and the specialist advisory group contained patient representation and through these two groups the patient perspective was taken into account in every aspect of the project.

As part of the development of the economic model structure, a focus group was held on 26 February 2015 with two clinicians (nephrologists) and two patient representatives with experience of chronic kidney failure. The primary aim of this session was to understand the care pathway for patients diagnosed with AKI in the ICU and the focus of the discussion was on developing a diagrammatic representation of the patient pathway for someone experiencing AKI in the ICU. The findings from this session were used to inform the development of the structure of the decision model. In addition to the focus group, the final structure and parameter estimates used for the decision model were determined via iterative feedback from the project advisory board, which included a patient representative.

Chapter 2 Systematic review

Aim

The overall aim of this systematic review was to provide evidence to evaluate the potential for AKI diagnostics to enhance the NHS care of patients admitted to critical care. The review involved three searches designed to meet specific project objectives:

1. search 1: to identify candidate or in-development relevant diagnostic tests that could be used in critical care to identify AKI (horizon scanning)
2. search 2: to identify current evidence on the clinical utility, analytical validity and cost-effectiveness of diagnostic tests identified in search 1
3. search 3: to gather information to describe the clinical care pathway and standard care for AKI in critical care, including investigation, clinical management, interventions, health-care resource use, morbidity, mortality, quality of life and other relevant outcome descriptors (methods and findings reported in *Chapter 5*).

Search 1: horizon scanning

Objective

The objective of this search was to identify candidate or in-development relevant diagnostic tests that could be used in critical care to identify AKI.

Identification of studies

A broad strategy was employed to support a horizon-scanning search for tests and biomarkers that are, or can be, used for AKI diagnosis but that are not currently used as standard practice in emergency and critical care. Our search included ongoing studies in trials registers, conference proceedings and recently published studies in PubMed to ensure that all emerging test and biomarker evidence was identified. Inclusion of the major databases such as MEDLINE, EMBASE and Science Citation Index (via Web of Science) enabled comprehensive identification of relevant literature and allowed assessment of the likely weight of evidence (volume of research) for different tests should they be included in the next stage (search 2, evidence on candidate tests). Searches were carried out in September 2014 in ClinicalTrials.gov (US National Institutes of Health) (accessed 29 September 2014), Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 9 of 12, September 2014), Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 9 of 12, September 2014), Conference Proceedings Citation Index – Science (Thomson Reuters' Web of Science) (1990 to September 2014), Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 3 of 4, July 2014), EMBASE Classic and EMBASE (via Ovid) (1947 to 25 September 2014), International Clinical Trials Registry Platform (World Health Organization) [www.who.int/ictrp/en/ (accessed 29 September 2014)], MEDLINE (via Ovid) (1946 to September Week 3 2014), MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (25 September 2014), *meta*Register of Current Controlled Trials (*m*RCT) (accessed 29 September 2014), PubMed (US National Library of Medicine) (1946 to September 2014) and Science Citation Index (Thomson Reuters Web of Science) (1900 to September 2014).

The search terms included index terms, free-text words, abbreviations and synonyms. Terms for AKI and specific biomarkers were identified from known relevant papers, database thesauri and suggestions from clinical members of the team. Searches for diagnostic studies are known to often retrieve very large numbers of citations. Although the use of diagnostic search filters is cautioned against – because of poor reporting and indexing – for pragmatic reasons we included some diagnostic terms in these scoping

searches. We combined our search concept for AKI with a 'fluid' search concept as only tests using fluid samples (rather than tissue samples) could be considered for use in emergency and critical care. A variety of terms, headings and subheadings were combined to identify 'tests'. The concepts used were:

1. AKI or conditions that imply AKI (e.g. tubular necrosis)
2. diagnostic tests or biomarkers [generic 'test' terms; MeSH terms, e.g. Acute-Phase Proteins/du (Diagnostic use); specific test terms, e.g. NGAL]
3. plasma, blood, urine and serum samples or specimens
4. evaluation of a test to predict or diagnose (e.g. sensitivity, accuracy, monitor, etc.).

The research team agreed that biomarkers developed and evidence gathered during the previous 10 years would be most relevant for the scoping review. All sources were searched from 2004 onwards, except for Web of Science, which was searched from 2008 onwards. The complete search strategies are available in *Appendix 1*.

Selection of studies

Studies were included if the participants were adults or children with new or existing AKI and (1) they were based in critical care (or another clinical setting if using a candidate test for future use in clinical care), (2) they evaluated a fluid biomarker not currently used as part of routine care for AKI, (3) they used the biomarker for AKI diagnosis, risk stratification or prediction of treatment benefit and (4) they involved at least 52 subjects. The participant criterion was based on the hypothesis that useful biomarkers in the literature have been evaluated in underpowered studies. Thus, we made the following assumptions: in order to be published, markers have a sensitivity and specificity of 0.6; to be inclusive in terms of power $(1 - \beta)$ and significance level (α), we assumed power to be 0.7 and the significance level to be 0.2; and ideally a marker would be most useful if it had a sensitivity and specificity of 0.7 or 0.8 (although 0.8 is unlikely). To identify the most relevant literature, we anticipated that the majority of early-stage clinical validation studies would have equal numbers of cases and controls. In addition, to include studies with some chance of identifying markers with a sensitivity/specificity of > 0.8, we selected papers that studied at least 52 patients (26 per arm in trials) (*Table 1*).

Studies were excluded if the participants had CKD only, if they used a tissue biomarker or imaging technology for AKI diagnosis, or if the biomarker was used only for monitoring events subsequent to an AKI diagnosis (e.g. post discharge). Biomarker discovery and preclinical studies were also excluded, along with those evaluating the stability and/or storage of biomarker samples. No restrictions on language or study design were applied (*Table 2*).

Literature yield

Scoping searches conducted at the project proposal stage suggested a pool of around 2500 references; however, the final search identified 6329 articles, which was reduced to 4804 following exclusion of duplicates. Given this almost twofold increase in the volume of literature, and in a change to the protocol, the decision was taken to appraise articles in a single stage (title and abstract screen) rather than in two

TABLE 1 Patients numbers for a range of sensitivities and specificities

Sensitivity and specificity	Number (non-AKI)	Number (AKI)	Number (total)
0.65	467	467	934
0.70	113	113	226
0.75	48	48	96
0.80	26	26	52
0.85	15	15	30
0.90	10	10	20

TABLE 2 PICOS (*p*opulation, *i*nterventions, *c*omparator, *o*utcomes, *s*tudy design) criteria for search 1: horizon scanning

PICOS criteria	Inclusion criteria	Exclusion criteria
*P*opulation	• Adults and children with new or existing AKI • Critical care (or other clinical setting if the test is a future candidate for critical care) • Participant group ≥ 52 (≥ 26 per arm if a trial)	• Animal-only studies • Adults and children with CKD only • Participant group < 52 (< 26 per arm if a trial)
*I*nterventions	• Fluid biomarker (e.g. urine, plasma, blood) • Not currently used in routine care (for AKI) • Utilised for diagnosis or decision-making related to AKI • Evaluated to determine clinical validity	• Tissue biomarker or imaging technology • Designed or used only for monitoring of events subsequent to a diagnosis of AKI (e.g. post discharge from hospital) • Biomarker discovery and preclinical studies • Evaluation of stability and/or storage of samples for biomarkers
*C*omparator	• None or an alternative biomarker	• None
*O*utcomes	• Diagnosis of new-onset AKI • Risk stratification in diagnosed AKI • Treatment benefit prediction in diagnosed AKI	• None
*S*tudy design	• Systematic review, RCT, clinical trial, observational, qualitative or acceptability study, economic evaluation • Published abstract if sufficient clinical, cost or outcome data presented in lieu of a full paper	• Commentary • Editorial • Letter (unless research letter reporting data)

stages (title and abstract screen followed by full-text review). At the outset of the process, a training session was held to facilitate standardisation in screening and selection and ensure that each reviewer was aware of and understood the explicit inclusion and exclusion criteria. Abstracts were then screened for relevance by individual reviewers (with independent double assessment of 25% of articles), with 487 relevant articles identified.

Identification of candidate biomarkers

Data from each of the 487 studies were extracted by one reviewer (EDM) and used to produce a longlist of potential biomarkers. In total, 153 individual biomarkers (excluding serum creatinine) were identified. Non-novel biomarkers, that is, those that were already used as part of standard care in the diagnosis of kidney function, were excluded ($n = 11$), as were those for which the citation did not report complete details of the population studied ($n = 19$). The remainder (see *Appendix 2*) were then tabulated on four dimensions: volume of evidence, currency of evidence, total population included and biological or mechanistic plausibility (inflammatory marker, function marker, damage marker and cell cycle marker). Pragmatic limits were then set on each of the dimensions to enable the longlist to be reduced while trying to ensure that the focus of search 2 would be on those tests that would be likely to produce the most evidence. The limits and their rationales were as follows:

- the biomarker must have been considered in six or more studies – to try to ensure that there were sufficient data to allow appropriate synthesis for each test
- studies must have been published in the previous 5 years – to try to ensure that only the most promising biomarkers with recent evidence were included
- the biomarker must have been used with ≥ 1500 subjects in total (i.e. across studies) – to try to ensure that the biomarker had wide clinical use and would provide sufficient data for synthesis
- biomarkers from all four plausibility dimensions should be represented – to ensure that the focus did not exclude biomarkers with a specific biological or mechanistic function.

Application of these limits provided a shortlist of 10 candidate tests (*Table 3*), which, following review by the Project Delivery Board and ratification by the specialist advisory group, were used in search 2.

TABLE 3 Candidate biomarkers for inclusion in search 2

Biomarker	Studies (*n*)	Subjects (*n*)	Biology/mechanism
BNP	6	3402	Functional marker
Cystatin C	73	21,180	Functional marker
IL-6	8	33,224	Inflammatory marker
IL-18	40	15,965	Inflammatory marker
KIM-1	40	12,959	Damage marker
L-FABP	28	7865	Functional marker
NAG	20	2982	Cell cycle marker
Nephrocheck (TIMP-2 and IGFBP-7)	6	1817	Cell cycle marker
NGAL	173	52,763	Inflammatory/damage marker
TNF-α	6	31,090	Inflammatory marker

BNP, brain natriuretic peptide; NAG, *N*-acetyl-beta-D-glucosaminidase; TNF-α, tumour necrosis factor alpha.

Search 2: identification of evidence for candidate tests

Objective

The objective of this search was to identify current evidence on the analytical validity, clinical validity, clinical utility and cost-effectiveness of the diagnostic tests identified in search 1.

Identification of studies

The world literature from 2004 to November 2015 was reviewed to identify existing research describing the diagnostic accuracy, analytical validity or cost-effectiveness of the 10 candidate biomarkers. It became clear when developing our search strategy that we would identify considerably more literature than suggested by our prestudy scoping searches. We therefore took the decision to carry out a more sensitive search over a shorter time period rather than a precise search covering the full duration of the databases. As our aim was to identify novel tests, we believed that this approach would be more inclusive, identifying the diversity of newer biomarkers and reducing the identification of older, established biomarkers. We searched the following databases for published and unpublished literature: ClinicalTrials.gov (US National Institutes of Health) (accessed 30 November 2015), Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 10 of 12, October 2015), Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 11 of 12, November 2015), Conference Proceedings Citation Index – Science (Thomson Reuters Web of Science) (1990 to November 2015), Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 2 of 4, April 2015), EMBASE Classic and EMBASE (via Ovid) (1947 to 24 November 2015), Health Technology Assessment database (via Wiley Online Library) (Issue 4 of 4, October 2015), Health Management Information Consortium database (1983 to November 2015), International Clinical Trials Registry Platform (World Health Organization) (accessed 30 November 2015), MEDLINE (via Ovid) (1946 to November Week 2 2015), MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (24 November 2015), NHS Economic Evaluation Database (via Wiley Online Library) (Issue 2 of 4, April 2015), PubMed (US National Library of Medicine) (1946 to November 2015) and Science Citation Index (Thomson Reuters Web of Science) (1900 to November 2015).

The search consisted of index terms and text words for AKI, AKI synonyms and name variants for the 10 biomarkers: brain natriuretic peptide (BNP), cystatin C, IL-18, IL-6, KIM-1, L-FABP, *N*-acetyl-beta-D-glucosaminidase (NAG), Nephrocheck, NGAL and tumour necrosis factor alpha (TNF-α). The searches were limited by date of publication (from 2004) but no restrictions on language were applied (non-English-language papers were included at this stage but would be included for full-text assessment only if translation of the

study data would be possible within the project timescale). All study designs except for single case studies were included. A diagnostic search filter was tested but not used in the final searches as it excluded potentially relevant abstracts. Search strategies for each database are provided in *Appendix 3*.

Selection of studies

Studies were included if they evaluated at least one of the outcome areas of clinical validity (including utility), analytical validity or cost-effectiveness and:

- the participants were adults or children with new or existing AKI
- they were based in critical care or the emergency department or included patients undergoing cardiac surgery
- they evaluated one or more of the 10 candidate biomarkers (fluid only)
- they included serum creatinine or another candidate biomarker as a comparator
- they assessed use of the biomarker for AKI-related decision-making
- they involved at least 50 subjects (unless reporting an aspect of analytical validity or cost-effectiveness).

The emergency department and cardiac surgery (including presurgery) were included as the most important alternative settings to consider when trying to capture relevant tests used outside ICUs/high-dependency units that might be transferable to the critical care setting. A cut-off point of ≥ 50 participants was used to include studies with some chance of identifying markers with a sensitivity/specificity of > 0.75 (see *Table 1*). This threshold was lowered slightly from search 1 to be as inclusive as possible when obtaining evidence relevant to the candidate biomarkers.

Studies were excluded if they involved kidney transplant patients only, studied a tissue biomarker or imaging technology for AKI diagnosis or used the biomarker only for predicting transplant rejection. Studies considering risk factors for AKI itself or combining the results for individual tests (with the exception of algorithmic biomarkers) were also excluded, as were case studies and descriptive or commentary pieces (*Table 4*).

Identified citations were stratified according to the test under study and in relation to whether they considered single or multiple biomarkers and were reviewed on a group-by-group basis. Titles and abstracts were screened for eligibility by one reviewer, with a random sample (15%) of articles independently screened by a second reviewer. Full-text articles of potentially relevant studies were then obtained and independently assessed by two reviewers to determine their inclusion status. Differences of opinion were discussed until a consensus was reached. To facilitate consistency in appraisal, the three main reviewers (EDM, NC and NW) initially assessed a batch of 14 papers independently and then met to discuss outcomes and to ensure clarity around the inclusion and exclusion criteria.

Data extraction

Data extraction was carried out by a single reviewer using a bespoke proforma (see *Appendix 4*). Data extracted included study methodology, country of study, study duration, setting and patient population (including baseline characteristics), type of candidate test and parameters, details of the diagnostic 'gold standard' and AKI classification system used, outcome measure(s) studied and findings. Analytical and validation factors associated with the physical measurement of a biomarker [including sensitivity, specificity, precision, parallelism, recovery, selectivity, limit of quantitation (LOQ) and vulnerability to interferences] were also sought for review in line with current US Food and Drug Administration (FDA) best practice guidelines[18] and Clinical and Laboratory Standards Institute (CLSI) principles (see *Table 38*).[29] Pre-analytical variables that might influence the quality, integrity or composition of samples, including biological factors (such as within-patient variability, sample timing, medical history and diet and lifestyle) and technical factors (such as sample collection, processing, shipping and storage conditions), were also obtained. Prior to use, the data extraction proforma was piloted by the reviewers and team statisticians on a small number of studies and refined where necessary. Once the process of data extraction began, the statisticians then reviewed a sample of completed proformas to ensure that the relevant data were being extracted.

TABLE 4 PICOS (*p*opulation, *i*nterventions, *c*omparator, *o*utcomes, *s*tudy design) criteria for search 2: evidence for candidate tests

PICOS criteria	Inclusion criteria	Exclusion criteria
*P*opulation	• Adults and children with new or existing AKI • Participant group ≥ 50 (≥ 25 per arm if a trial) • Critical care setting • Cardiac surgery setting (including presurgery) • Any setting (analytical only) • Any participant number (analytical only)	• Animal-only studies • Transplant patients only • Participant group < 50 (< 25 per arm if a trial)
*I*nterventions	• Fluid biomarker • Used for diagnosis of AKI • Used for decision-making in AKI (treatment, prognosis etc.)	• Biomarker not specified in detail • Used to predict transplant rejection only
*C*omparator	• Creatinine • Alternative candidate biomarker • None (analytical or costs only)	• None
*O*utcomes	Primary: • diagnosis of AKI (plus one or more of a–d): (a) clinical validity (b) clinical utility (c) cost-effectiveness (d) analytical validity Secondary: • length of stay • readmission • recovery of kidney function • CKD • RRT • mortality	• Risk factors for AKI only • Combines results for individual biomarkers [does not include algorithmic biomarkers (e.g. Nephrocheck)]
*S*tudy design	• Systematic review, RCT, clinical trial, observational, qualitative or acceptability study, economic evaluation • Published abstract if sufficient clinical, cost or outcome data presented in lieu of a full paper	• Duplicate study • Case study • Editorial • Commentary (including non-systematic review) • Letter (unless research letter reporting data)

Quality assessment

Quality assessment for the evidence synthesis was carried out by one main reviewer (EDM) using the QUADAS-2 (quality assessment of diagnostic accuracy studies) tool,[30] a diagnostic test-specific approach to determine potential study bias. In this system, papers are evaluated on the basis of patient selection, interpretation of the index test, appropriateness and interpretation of the reference standard and flow of patients and timing of tests. The applicability of each study to the question under review is also assessed (see *Appendix 5*). In keeping with good practice, studies at risk of bias were not excluded from the meta-analysis. Instead, an appraisal of the strength of the existing evidence has been reported and the findings are interpreted in light of this.

Results of the systematic review

As was the case with search 1, broadening the search strategy to include tests used following cardiac surgery impacted significantly on the volume of literature identified compared with that anticipated by the original scoping strategy, with a total of 5045 articles identified. Given the time implications associated with assessment and data extraction in a complex review such as this, we took the decision to focus initially on three of the candidates: a recently developed test that is receiving considerable marketing and is the only FDA-licensed test for AKI (Nephrocheck, which detects two biomarkers, TIMP-2 and IGFBP-7) and the two biomarkers for which there was the greatest amount of evidence (cystatin C and NGAL).

The choice of these three tests as the focus for study was ultimately a pragmatic one, determined with advice from the specialist advisory group. Although fewer studies have used Nephrocheck than some of the other shortlisted tests, it is one of the most recent biomarkers that has shown enough promise to be approved by the FDA and so there is much interest in its clinical utility. We were aware that there would be more publications on the older biomarkers; however, our approach seemed an intelligent approach that avoided ignoring a new and potentially novel biomarker. Between them, these markers were considered in 3260 of the identified citations (65%), with 605 articles meeting the inclusion criteria for detailed review (*Figure 2*). We were unable to locate three papers and 23 non-English-language papers were set aside. Most of the excluded studies were either conference abstracts with no subsequent publication or studies that did not focus on the population or setting under review (*Table 5*). In total, 207 eligible papers[31–237] were included in the review (see *Appendix 6*).

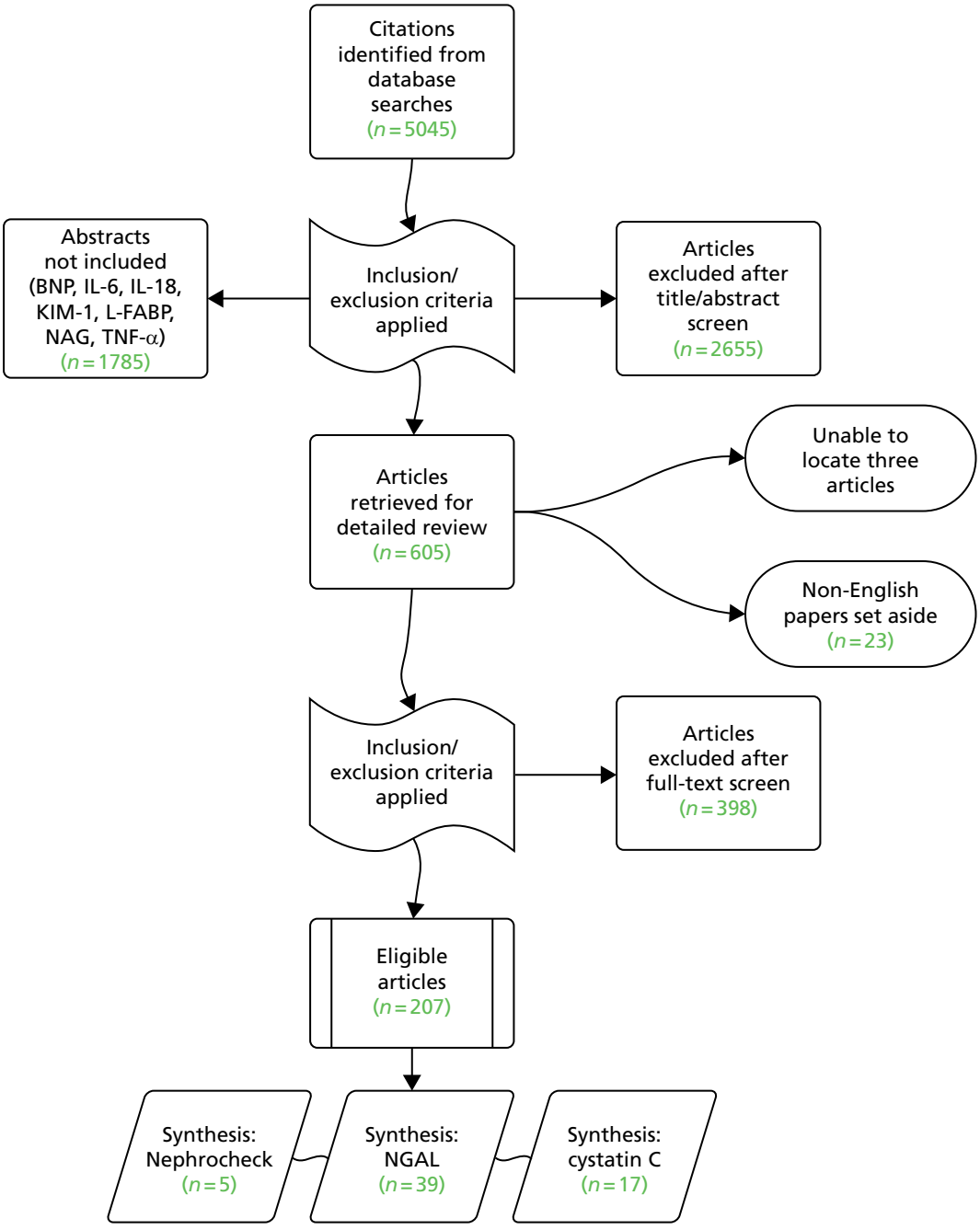

FIGURE 2 Flow of studies into the review.

TABLE 5 Reasons for study exclusion ($N = 398$)

Reason for exclusion	Number of studies
Abstract only (no full text available)	184
Outside the review setting	73
Not used for AKI diagnosis or decision-making	35
Participant group < 50	27
Non-English language	23
No discrete biomarker data	12
Duplicate paper or study	10
Review or meta-analysis (references checked)	9
No candidate biomarker studied	4
Editorial, commentary or letter	3
No comparator test included	3
Ongoing trial with full text identified	3
Study of transplant patients	3
Unable to obtain article	3
Animal study	2
Erratum only	2
Poster only (no full text available)	1
Study of patients with CKD	1

Location and setting

The majority of the eligible studies were carried out in Europe ($n = 114$, 55%) and North America ($n = 63$, 30%), with the USA being the single most prolific country (*Table 6*). Fifteen studies involved centres in multiple countries. The most commonly reported clinical setting was cardiac care ($n = 86$, 42%) – including 11 studies on contrast-induced nephropathy – followed by critical care ($n = 85$; 41%), the emergency department ($n = 20$; 10%) and the laboratory ($n = 11$, 5%). The setting of five studies was unclear. Less than one-quarter of studies ($n = 46$, 22%) reported the involvement of multiple centres (median 3, range 2–35) (see *Appendix 6*). Study duration ranged from 1 month to 7 years and most papers were published between 2012 and 2015 (70%).

Population

Most studies were small in scale (mean 227, median 112 participants), with the smallest being an analytical validity study involving 17 patients undergoing surgery for congenital heart disease and the largest being a study of 1635 adults admitted to the emergency department (see *Appendix 6*). Two studies

TABLE 6 Included papers by country under study

Country	Number of papers (%)
Argentina	1 (0.5)
Australia	9 (4.3)
Austria	3 (1.4)
Belgium	6 (2.9)

TABLE 6 Included papers by country under study (*continued*)

Country	Number of papers (%)
Bosnia and Herzegovina	1 (0.5)
Brazil	3 (1.4)
Canada	9 (4.3)
China	14 (6.8)
Curaçao	1 (0.5)
Denmark	3 (1.4)
Egypt	5 (2.4)
Finland	5 (2.4)
France	11 (5.3)
Germany	17 (8.2)
Greece	4 (1.9)
Hungary	1 (0.5)
India	2 (1.0)
Iran	4 (1.9)
Ireland	1 (0.5)
Italy	12 (5.8)
Japan	5 (2.4)
Republic of Korea	10 (4.8)
Malaysia	1 (0.5)
The Netherlands	8 (3.9)
New Zealand	5 (2.4)
Pakistan	1 (0.5)
Poland	3 (1.4)
Portugal	3 (1.4)
Saudi Arabia	1 (0.5)
Serbia	3 (1.4)
Spain	8 (3.9)
Sri Lanka	1 (0.5)
Sweden	10 (4.8)
Switzerland	1 (0.5)
Taiwan	2 (1.0)
Thailand	1 (0.5)
Turkey	7 (3.4)
UK	7 (3.4)
USA	54 (26.1)

Fifteen studies involved multiple locations and have been listed under each included country: Austria, Belgium, Canada, France, Germany, Spain, Sweden, the UK and the USA ($n = 1$); Austria, Belgium, France, Germany, Spain, Sweden, the UK and the USA ($n = 2$); Belgium, France ($n = 1$); Belgium and the USA ($n = 1$); Canada, the Netherlands and the USA ($n = 1$); Canada and the USA ($n = 5$); France, Italy and the USA ($n = 1$); Germany and the USA ($n = 1$); Italy and the USA ($n = 1$); Sri Lanka and the USA ($n = 1$).

did not specify population size: one on the analytical validity of NGAL and the other using decision analysis to model the cost-effectiveness of NGAL following cardiac surgery. In more than three-quarters of studies the population was adult patients ($n = 166$, 80%), with three studies including both adults and children. The source of the samples was not specified in two studies on the analytical validity of NGAL.

Biomarkers and outcome areas

The most commonly studied biomarker was NGAL ($n = 145$, 70%) followed by cystatin C ($n = 91$, 44%) and Nephrocheck ($n = 10$, 5%). One study evaluated all three tests, 35 evaluated cystatin C and NGAL and three evaluated Nephrocheck and NGAL. The Nephrocheck test is carried out using urine only, but cystatin C and NGAL were evaluated on a range of sample matrices, most commonly serum for cystatin C and urine for NGAL (*Table 7*). Forty-one studies evaluated two different matrices for the same or multiple biomarkers ($n = 14$ for cystatin C, $n = 35$ for NGAL). Although there is a standard definition for the diagnosis of AKI, various classifications can be used in clinical practice to grade the level of injury (*Table 8*). In this review, the most commonly used criteria in studies determining clinical validity were the RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease) criteria,[241] either alone or in conjunction with the Acute Kidney Injury Network (AKIN) criteria[242] ($n = 80$, 42%). Almost one-fifth of studies did not report using one of the standard classifications.

Of the outcomes areas evaluated in this review, the most commonly considered was clinical validity (i.e. diagnostic accuracy; $n = 193$, 93%). A smaller number of studies focused on analytical validity ($n = 12$, 6%), with only two studies focusing on the cost-effectiveness of biomarker use (both in cardiac surgery, one looking at NGAL use in adults and the other looking at the use of cystatin C and NGAL in children). Almost one-quarter of studies ($n = 46$, 22%) reported on clinical validity alongside some aspect of analytical validity, usually related to brief details on limits of detection or inter-/intra-assay variation. In most of the studies dealing with clinical validity, the purpose of the use of the biomarker was AKI diagnosis, either solely ($n = 126$; 65%) or alongside risk prediction ($n = 34$, 18%) or prognosis ($n = 21$, 11%).

Quality assessment

With few exceptions, a cohort study design was the most frequently used study design in biomarker evaluation ($n = 181$, 87%), perhaps unsurprisingly given the topic under review. There were four RCTs, all of them relatively small scale ($n = 71$–204 adult patients), one in critical care and three involving cardiac surgery. One paper reported subgroup analysis from a larger trial but did not provide details of the parent study; the focus of two others was on the use of therapeutic drug treatment to prevent renal damage [Probucol (Sanofi Aventis, Paris, France) and erythropoietin].

Only 14% of studies ($n = 29$) reported a power calculation to justify the included sample size and less than half provided details of patient throughout [$n = 88$, 43%; Consolidated Standards of Reporting Trials (CONSORT) diagram, $n = 38$; written statement, $n = 50$]. For the most part, the reporting of methodology was poor and few studies stated that they had adhered to a quality standard when describing their study [Standards for Reporting Diagnostic Accuracy (STARD) guidance,[243] $n = 4$; Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidance,[244] $n = 3$; both STARD and STROBE, $n = 1$].

TABLE 7 Biomarker evaluation by sample matrix used

	Biomarker		
Sample matrix	Cystatin C	Nephrocheck	NGAL
Plasma	23	–	51
Serum	54	–	23
Urine	27	10	105
Whole blood	–	–	2
Not specified	1	–	1

TABLE 8 Classifications for staging AKI in clinical validity studies ($N = 193$)

First author and year	Criteria	Studies,[a] *n* (%)
Definition of AKI	Absolute increase in SCr of ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours *or* a percentage increase of at least 50% (1.5 times the baseline value) *or* reduced urine output for > 6 hours (< 0.5 ml/kg/hour)	–
RIFLE[241]	R: ≥ 1.5- and < 2-fold increase from baseline SCr *or* ≥ 25% fall in GFR from baseline *or* urine output < 0.5 ml/kg/hour for ≥ 6 and < 12 hours	80 (41.5)
	I: ≥ 2- and < 3-fold increase from baseline SCr *or* ≥ 50% fall in GFR from baseline *or* urine output < 0.5 ml/kg/hour for ≥ 12 hours and < 24 hours	
	F: ≥ 3-fold increase from baseline SCr *or* ≥ 75% fall in GFR from baseline *or* SCr ≥ 4 mg/dl with an acute rise of ≥ 0.5 mg/dl *or* urine output < 0.3 ml/kg/hour for ≥ 24 hours *or* anuria for ≥ 12 hours	
	L: complete loss of renal function for > 4 weeks	
	E: end-stage renal disease	
AKIN[242]	Stage 1: increase in SCr of ≥ 0.3 mg/dl (≥ 26.4 µmol/l) *or* increase in SCr to ≥ 150–200% (1.5- to 2-fold) of baseline value *or* urine output < 0.5 ml/kg/hour for ≥ 6 and < 12 hours	62 (32.1)
	Stage 2: increase in SCr to > 200–300% (> 2- to 3-fold) of baseline value *or* urine output < 0.5 ml/kg/hour for ≥ 12 hours and < 24 hours	
	Stage 3: increase in SCr to > 300% (3-fold) of baseline value *or* SCr ≥ 4.0 mg/dl (≥ 354 µmol/l) with an absolute increase of ≥ 0.5 mg/dl (≥ 44 µmol/l) *or* initiation of RRT *or* urine output < 0.3 ml/kg/hour for ≥ 24 hours *or* anuria for ≥ 12 hours	
KDIGO (Kidney Disease: Improving Global Outcomes)[238]	Stage 1: 1.5–1.9 × baseline SCr *or* ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase in SCr *or* urine output < 0.5 ml/kg/hour for ≥ 6 and < 12 hours	26 (13.5)
	Stage 2: 2.0–2.9 × baseline SCr *or* urine output < 0.5 ml/kg/hour for ≥ 12 hours and < 24 hours	
	Stage 3: 3.0 × baseline SCr *or* increase in SCr of ≥ 4.0 mg/dl (≥ 353.6 µmol/l) *or* initiation of RRT *or*, in patients aged < 18 years, decrease in eGFR to < 35 ml/minute/1.73 m^2 *or* urine output < 0.3 ml/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours	
Other[b]	–	35 (18.1)
Not reported	–	4 (2.1)

eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; SCr, serum creatinine.
a 12 studies used the RIFLE and AKIN criteria and one study used the AKIN, KDIGO and RIFLE criteria.
b Includes the Acute Dialysis Quality Initiative Group consensus ($n = 4$),[239] the Kidney Disease Outcomes Quality Initiative guidelines[240] ($n = 1$) and the National Kidney Foundation guideline[240] ($n = 1$).

Fewer than two-thirds of clinical validity studies provided sensitivity and specificity data for a given biomarker cut-off threshold ($n = 113$, 59%). Only 42 eligible studies (20%) provided sufficient data to allow population of a confusion matrix and, therefore, their inclusion in meta-analysis: four studies evaluating Nephrocheck, 17 studies evaluating cystatin C and 35 studies evaluating NGAL (see *Chapter 3*).

Risk of bias among studies included in the evidence synthesis

When considered across the four domains – patient selection, index test, reference standard and flow and timing – only six[45,48,50,54,58,66] of the studies included in the evidence synthesis had a low risk of bias for all; two studies[49,72] did not report enough information to be able to allocate a level of bias for any of the domains (*Table 9*). Three studies had a high risk of bias for one domain: one[36] that used a prespecified threshold for the biomarker cut-off point (potential index test bias), one in which the analysis did not include all patients[39] and one that had a prolonged interval between the tests (both flow and timing bias).[57] In all of the remaining studies ($n = 31$, 74%), the level of bias was unclear in at least one of the domains. This was especially true for bias related to the reference standard, for which just over half of

TABLE 9 Risk of bias among studies included in the evidence synthesis

First author and year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ayodogdu 2013[32]	✓	?	✓	✓	✓	✓	✓
Bihorac 2014[33]	?	✓	✓	✓	✓	✓	✓
Chen 2012[34]	✓	?	✓	✓	✓	✓	✓
Cho 2013[35]	✓	?	✓	✓	✓	✓	✓
Constantin 2010[36]	✓	✗	✓	✓	✓	✓	✓
de Geus 2011[37]	✓	?	✓	✓	✓	✓	✓
Ghonemy 2014[38]	?	?	✓	✓	✓	?	✓
Haase 2009[31]	?	?	?	✓	?	?	✓
Haase-Fielitz 2009[39]	?	✓	?	✗	?	✓	?
Haase-Fielitz 2009[40]	?	?	✓	✓	✓	✓	✓
Han 2009[41]	✓	?	?	✓	✓	?	✓
Herget-Rosenthal 2004[42]	✓	?	?	✓	✓	✓	✓
Hjortrup 2015[43]	?	✓	?	?	✓	✓	✓
Hoste 2014[44]	✓	✓	?	✓	✓	✓	✓
Kashani 2013[45]	✓	✓	✓	✓	✓	✓	✓
Kato 2008[46]	✓	?	?	✓	✓	?	✓
Kidher 2014[47]	?	?	✓	✓	✓	✓	✓
Kokkoris 2012[48]	✓	✓	✓	✓	✓	✓	✓
Legrand 2015[49]	?	?	?	?	?	?	?
Liangos 2009[50]	✓	✓	✓	✓	✓	✓	✓
Linko 2013[51]	✓	?	?	?	✓	✓	?
Liu 2013[52]	?	✓	✓	✓	✓	✓	✓
McIlroy 2010[53]	?	?	✓	✓	✓	✓	✓
Meersch 2014[54]	✓	✓	✓	✓	✓	✓	✓
Meersch 2014[55]	✓	?	✓	✓	✓	✓	✓
Munir 2013[56]	✓	?	✓	✓	✓	✓	✓
Nejat 2010[57]	✓	?	?	✗	✓	✓	✓
Oh 2012[58]	✓	✓	✓	✓	✓	✓	✓
Palazzuoli 2015[59]	✓	?	?	✓	✓	✓	✓
Parikh 2011[60]	?	✓	✓	✓	✓	✓	✓
Park 2015[61]	✓	?	✓	✓	✓	✓	✓
Perrotti 2015[62]	✓	?	?	?	✓	✓	✓
Perry 2010[63]	?	✓	✓	✓	✓	✓	✓
Prowle 2015[64]	?	✓	✓	✓	✓	✓	✓
Sargentini 2012[65]	?	?	?	✓	✓	✓	✓
Shum 2015[66]	✓	✓	✓	✓	✓	✓	✓

TABLE 9 Risk of bias among studies included in the evidence synthesis (*continued*)

First author and year	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Tuladhar 2009[67]	✓	?	?	?	✓	✓	✓
Tung 2015[68]	✓	?	?	✓	✓	✓	✓
Tziakas 2015[69]	✓	?	?	?	✓	✓	✓
Varela 2015[70]	?	?	?	✓	✓	✓	✓
Villa 2005[71]	?	?	?	✓	✓	✓	✓
Wagener 2008[72]	?	?	?	?	✓	✓	✓

✓, low risk of bias; ✗, high risk of bias; ?, unclear risk of bias.

studies ($n = 22$, 52%) did not provide information on blinding, that is, whether or not the index test results were interpreted without knowledge of the results of the reference standard. There was little concern that the included studies were not applicable to this review.

Discussion

This review was undertaken to provide a comprehensive picture of the current evidence around the clinical and analytical validity and cost-effectiveness of novel biomarkers for the diagnosis of AKI in critical care. There is undoubtedly a considerable amount of research in this area; however, issues related to the quality of reporting meant that less than one-quarter of the eligible studies identified were able to be included in meta-analysis. In addition, this made it difficult to determine the levels of potential bias across studies.

Several key issues were encountered when carrying out this piece of work. First, in the absence of published guidance, the test shortlisting criteria were developed by expert consultation and, as such, may not have captured all of the promising in-development tests because of the pragmatic focus on objective criteria (such as volume of evidence). Second, the literature yield was substantially greater than originally indicated by the prestudy scoping searches, largely because of the decision to broaden the final scope to include tests developed outside the critical care setting. This, combined with the number of candidate tests identified (including multiple tests evaluated in the same study) and the complexity of data extraction (which sought to determine both clinical and analytical validity), resulted in extended study timelines and an inability to complete the review for all 10 candidate biomarkers. Furthermore, differences in inclusion and exclusion criteria depending on whether the focus was on clinical or analytical validity made it more difficult to exclude potentially irrelevant studies at the abstract screening stage as this could not easily be achieved using sample size or the presence of a comparator (see *Table 4*). The decision to include an eligibility criterion based on sample size for studies with equal numbers of cases and controls could have been improved by stating that the group of interest (AKI in this case) had to be at least this size and the other group (no AKI) could have been larger.

As the number of biomarkers entering the health-care market continues to expand rapidly, the role of reviews to inform future research priorities is increasingly important. The two-stage search process outlined here represents a novel approach in this area; however, it is clear that further work is required to establish efficient and optimal search strategies and shortlisting criteria for such reviews.

Chapter 3 Meta-analysis of diagnostic tests for acute kidney injury

Introduction

In this chapter a meta-analysis of diagnostic accuracy studies is provided to evaluate the body of evidence available for three diagnostic tests of AKI and to provide input into the decision analysis in subsequent chapters. The primary health-care setting considered in the use of these tests was the critical care unit and the secondary health-care setting considered was cardiac surgery (pre and/or post intervention). The three diagnostic tests considered were the Nephrocheck test (which uses a combination of two proteins: TIMP-2 and IGFBP-7) and the biomarkers NGAL and cystatin C. The NGAL and cystatin C tests have been used in this setting for measurement of their concentration in samples of blood serum, blood plasma and urine and these media were considered separately. The pooled estimates of sensitivity and specificity and their variance from the meta-analyses directly informed the decision analysis in *Chapter 5*. In our searches we identified no previous reviews or meta-analyses considering Nephrocheck or cystatin C in this setting, but we did identify two relevant reviews of NGAL.[40,245]

Methods

Primary objective

The primary objective was to estimate pooled means and variances of sensitivity and specificity for each of the diagnostic tests considered. When appropriate data were available, these estimates were obtained separately for each of the health-care settings considered and for each of the sample media considered. When only one study was available, no meta-analysis was undertaken.

Identification of studies

Details on the search strategies used to identify studies and the process for study screening and evaluation, data extraction and quality assessment are presented in *Chapter 2*.

Full papers were retrieved for studies of all patients (< 18 years, ≥ 18 years) in which AKI diagnosis had been evaluated using any one or multiples of the three diagnostic tests considered (Nephrocheck, NGAL, cystatin C), in any of the sample media considered (blood serum, blood plasma or urine), in either of the health-care settings considered (critical care unit or cardiac surgery). Studies were excluded if they were not primarily located in either of these health-care settings.

Study methods

The gold standard for determining AKI diagnosis was defined as diagnosis according to the RIFLE,[241] AKIN[242] or KDIGO (Kidney Disease: Improving Global Outcomes)[238] diagnostic and classification system, based on an assessment of serum creatinine levels and urine output (see *Chapter 2*).

Outcome measurements

The primary outcomes were sensitivity (the probability of the test being positive given that the true diagnosis is positive) and specificity (the probability of the test being negative given that the true diagnosis is negative), which are determined by comparison of the results of the experimental diagnostic test with the results of the gold standard method used in the study. Studies were excluded if the gold standard method used to determine the outcome was not described in sufficient detail. Studies were not excluded if the cut-off point used to assess the positive and negative status of the outcome in the experimental diagnostic test was not reported.

Diagnostic and staging systems for acute kidney injury

A number of diagnostic and staging systems for AKI have been used in diagnostic accuracy studies. The most commonly used make use of repeated serum creatinine measurements and measurement of urine output to diagnose and stage AKI. Three commonly used systems are the RIFLE, AKIN and KDIGO systems.

RIFLE classification of acute kidney injury

The Acute Dialysis Outcome Initiative group proposed the RIFLE classification, which defines five categories of AKI,[241] as shown in *Table 8*. AKI is staged for severity according to the criteria listed in *Table 8*, with any classification of risk or above being a diagnosis of AKI.

Acute Kidney Injury Network classification of acute kidney injury

The AKIN has defined diagnostic criteria for AKI and provided a staging system for the severity of AKI,[242] as shown in *Table 8*. AKI is staged for severity according to the criteria listed in *Table 8*, with any classification of stage 1 or above being a diagnosis of AKI. In particular, in contrast to the RIFLE criteria, the absolute change in serum creatinine defining AKI is defined as an abrupt (within 48 hours) reduction in kidney function as defined by stage 1 or above.

KDIGO classification of acute kidney injury

The 2011 KDIGO Clinical Practice Guideline for AKI (Summary of Recommendation Statements, 2012)[246] defined diagnostic criteria for AKI and provided a staging system for the severity of AKI, as shown in *Table 8*. AKI is staged for severity according to the criteria listed in *Table 8*, with any classification of stage 1 or above being a diagnosis of AKI. This classification system uses the same time frame for absolute changes as the AKIN criteria and clarifies that for the relative changes the baseline values should be known or presumed to have occurred within the previous 7 days.

Summary of staging methods

There is a similarity between the staging and diagnostic criteria proposed for AKI, which is demonstrated in *Table 10*. It has been shown that the AKIN criteria can diagnose more patients correctly with AKI than the RIFLE criteria (not unexpected given the additional criterion – the absolute change in serum creatinine level), but it has not been shown to have a better predictive ability for in-hospital mortality.[247] It has also been shown that the AKIN criteria do not improve the sensitivity of AKI diagnosis compared with the RIFLE criteria in the first 24 hours after admission to the critical care unit.[248] Similarly, it has been shown than a higher incidence of AKI can be diagnosed using the KDIGO criteria than using the RIFLE criteria and that the KDIGO criteria are more predictive for in-hospital mortality, but there was no significant difference between the AKIN criteria and the KDIGO criteria.[249] Other studies have suggested that the RIFLE, AKIN and KDIGO criteria are good tools for predicting mortality in critically ill patients and observe no evidence of a difference between them.[250]

Based on the definitions used in the different diagnostic and staging/classification systems and the evidence above we believe that there are broad similarities between the RIFLE, AKIN and KDIGO criteria

TABLE 10 Comparison of common AKI diagnostic and staging/classification systems based on serum creatinine levels and urine output

Staging system	Stage or classification				
RIFLE	R	I	F	L	E
AKIN	1	2	3		
KDIGO	1	2	3		
			RRT		
	AKI 'diagnosis'		**AKI 'failure'**		

and, for the purposes of this study, we defined a diagnosis of AKI, following the KDIGO criteria, as any of the following:

- increase in serum creatinine of ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours
- increase in serum creatinine to ≥ 1.5 × baseline, which is known or presumed to have occurred within the previous 7 days
- urine volume < 0.5 ml/kg/hour for at least 6 hours.

Furthermore, in the studies identified for inclusion in the meta-analysis, studies that used either of the outcomes indicated by the shaded areas in *Table 10* (RIFLE R, AKIN 1 or KDIGO 1 – a diagnostic-type outcome; RIFLE F, AKIN 3, KDIGO 3 or RRT – a failure-type outcome) were considered homogeneous for the purposes of the meta-analysis.

Key data extracted

The primary data extracted for inclusion in the meta-analysis are shown in *Table 11*. It is recommended in the STARD statement that a cross-tabulation of the index test results by the results of the reference standard is included in any study report,[251,252] but it was anticipated that this information would not be present in all study reports. In this situation the elements of the confusion matrix were calculated using information describing the diagnostic outcomes and estimates of sensitivity and specificity. For example, if the sensitivity (s) and number of true diagnoses [given by the sum of the number of true positives (TPs) and the number of false negatives (FNs), i.e. (TP + FN)] were reported in the study then the number of TPs could be calculated as s.(TP + FN). A similar calculation for specificity (p) allowed the estimation of the number of true negatives (TNs): p.(FP + TN), where FP represents the number of false positives. Finally, given these estimates for TP and TN and the numbers of true outcomes [(TP + FN) and (FP + TN)], simple subtraction provided estimates for FN and FP.

Study exclusion

Studies were excluded from the meta-analysis if it was not possible to estimate values for the elements of the confusion matrix or if other key data could not be extracted. Further reasons for the exclusion of studies were if diagnosis was carried out in the emergency department rather than in the critical care unit and if the biomarker was measured on a relative scale rather than an absolute scale, for example unit of biomarker per unit of serum creatinine.

Data analysis

Simple diagnostic accuracy summaries [sensitivity, specificity and the diagnostic odds ratio (DOR) and its components – positive likelihood ratio (LR+) and negative likelihood ratio (LR–)] were produced for each study included in the meta-analysis. The sensitivity of a diagnostic test (T) is defined formally as the probability that the test will give a positive result if the patient has the disease (D+), in this case AKI. This is often referred to as the TP rate for a diagnostic test and can be expressed as a conditional probability:

$$s = \text{Sensitivity} = P(\text{test} = \text{positive} \mid \text{status} = \text{diseased}) = P(\text{T}+ \mid \text{D}+). \quad (1)$$

TABLE 11 Confusion matrix

	Test outcome			
True outcome	Test+	Test–	Diagnostic property	True outcome
Disease+ (D+)	TP	FN	Sensitivity = TP/(TP + FN)	TP + FN
Disease– (D–)	FP	TN	Specificity = TN/(TN + FP)	FP + TN
	TP + FP	FN + TN		

The specificity of a diagnostic test is the probability that the test will give a negative result if the patient does not have the disease (D–), which is equivalent to 1 minus the FP rate for the test and can be expressed as the conditional probability:

$$p = \text{Specificity} = P(\text{test} = \text{negative} \mid \text{status} = \text{not diseased}) = P(\text{T}- \mid \text{D}-). \quad (2)$$

Confidence intervals (CIs) were estimated for sensitivity and specificity based on the Wilson score interval method.[253]

The LR+ of a diagnostic test is the probability of a patient with disease (D+) having a positive test result divided by the probability of a patient without disease (D–) having a positive test result:

$$\text{LR}+ = P(T+ \mid \text{D}+)/P(\text{T}+ \mid \text{D}-). \quad (3)$$

Similarly, the LR– of a diagnostic test is the probability of a patient with disease having a negative test result divided by the probability of a patient without disease having a negative test result:

$$\text{LR}- = P(\text{T}- \mid \text{D}+)/P(\text{T}- \mid \text{D}-). \quad (4)$$

Confidence intervals for the LR+ and LR– were estimated using the method of Koopman.[254]

The DOR for a test is the ratio of the odds of a positive test result for a patient with disease relative to the odds of a positive test result for a patient without disease:

$$\text{DOR} = \text{LR}+ / \text{LR}-. \quad (5)$$

Confidence intervals for log(DOR) were estimated based on the assumption that, as an odds ratio, the DOR is normally distributed. Estimates for DOR were then obtained by back-transformation.

The method of meta-analysis for diagnostic accuracy studies used here was the bivariate meta-analysis proposed by Reitsma *et al.*,[255] based on the methodology of van Houwelingen *et al.*[256] Briefly, if logit sensitivity (μ_{si}) and logit specificity (μ_{pi}) are

$$\mu_{Si} = \text{logit}(s_i) = \log\left(\frac{s}{1-s}\right) \quad (6)$$

and

$$\mu_{Pi} = \text{logit}(p_i) = \log\left(\frac{p}{1-p}\right), i = 1, \ldots, k. \quad (7)$$

for each study i (with k studies included in the meta-analysis), the true logit sensitivity and logit specificity are then assumed to have a bivariate normal distribution across studies:

$$\begin{pmatrix} \mu_{Si} \\ \mu_{Pi} \end{pmatrix} \backsim N\left(\begin{pmatrix} \mu_S \\ \mu_P \end{pmatrix}, \Sigma_{SP}\right), \quad (8)$$

$$\text{where } \Sigma_{SP} = \begin{pmatrix} \sigma_S^2 & \sigma_{SP}^n \\ \sigma_{SP}^n & \sigma_P^2 \end{pmatrix}.$$

where σ_{SP}^n is the covariance between logit sensitivity and logit specificity. This model is extended by incorporating the variability due to sampling through the variance of sensitivity ($s_{S,i}^2$) and specificity ($s_{P,i}^2$), as measured in each study:

$$s_{S,i}^2 = \frac{1}{n_{S,i} p_{S,i} (1-p)_{S,i}} \quad (9)$$

and

$$s^2_{P,i} = \frac{1}{n_{P,i} p_{P,i} (1-p)_{P,i}}, \tag{10}$$

assuming that $0 < p$ and $s < 1$ and that the number of subjects used to estimate sensitivity and specificity is large.[256] The final model is then a bivariate random-effects model of the form:

$$\left(\frac{\mu_{Si}}{\mu_{Pi}}\right) \sim N\left(\left(\frac{\mu_S}{\mu_P}\right), \Sigma_{SP} + C_i\right), \tag{11}$$

where $C_i = \begin{pmatrix} s^2_{S,i} & 0 \\ 0 & s^2_{P,i} \end{pmatrix}$.

This model was estimated using likelihood-based methods using the mada package[257] in the R Environment for Statistical Computing (The R Foundation for Statistical Computing, Vienna, Austria). It has been shown that this method is equivalent to the hierarchical regression meta-analysis proposed by and further developed by Rutter and Gatsonis when there are no study-level covariates.[258–260]

Separate meta-analyses were conducted for each diagnostic test, sample media and health service setting. Pooled estimates of sensitivity, specificity, LR+, LR– and DOR can be estimated from back-transformed parameter estimates. Estimates from each study and pooled estimates from the meta-analysis are presented in forest plots. A summary receiver operating characteristic (SROC) curve was estimated, with estimates of the confidence and prediction region.[255,259] Approximate estimates of the variance of sensitivity and specificity for use in the economic model were determined using the delta method.[261]

Tests of heterogeneity were not used, as such statistical methods (Cochran's Q, I^2) do not account for heterogeneity explained by phenomena such as positivity threshold effects and are not recommended by the Cochrane Diagnostic Test Accuracy Group.[262] Estimating the prediction region in the SROC curve is one way of examining the extent of heterogeneity by depicting a region within which, assuming that the model is correct, we have 95% confidence that the true sensitivity and specificity of a future study would lie.[260]

Results

Papers selected for inclusion in the meta-analysis are described briefly in tabular summaries followed by a summary of diagnostic accuracy for each study. Pooled estimates of sensitivity and specificity and the SROC curve are also provided for each diagnostic test, health-care setting and sample type. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that depicts the flow of information through the different phases of the systematic review to data extraction and final inclusion in the meta-analysis is shown in *Chapter 2* (see *Figure 2*).

Nephrocheck

Critical care unit: plasma and serum

The searches identified no studies suitable for data extraction for this diagnostic test in either health-care setting for either plasma or serum.

Critical care unit: urine

Summaries of the baseline characteristics and test parameters for the included urinary Nephrocheck studies are shown in *Table 12*. Three studies were included,[33,44,45] with a total of 1289 patients [199 patients (15.4%) with a diagnosis of AKI and 1090 patients (84.6%) without a diagnosis of AKI]. The sample for use in the test was taken on enrolment in all of the included studies. The outcome used to define the

TABLE 12 Characteristics of studies included in meta-analysis for Nephrocheck in the critical care unit health-care setting using urine

First author and year	Patient group	Age (years)	Timing of test sample	Threshold	Outcome	Outcome	
						+	–
Kashani 2013[45]	Patients admitted to the critical care unit	Median (IQR): ± 64 (53, 73)	Within 18 hours of enrolment	0.3	KDIGO (2 or 3) within 12 hours	101	627
Bihorac 2014[33]	Patients admitted to the critical care unit	Mean (SD): ± 63 (17)	On enrolment (median 15 hours from admission)	0.3	KDIGO (2 or 3) within 12 hours	71	337
Hoste 2014[44]	Patients admitted to the critical care unit	Median (IQR): + 64 (54, 75); – 65 (54, 78)	On enrolment (within 24 hours of admission)	0.3	KDIGO (2 or 3) within 12 hours	27	126

+, with a diagnosis of AKI; –, without a diagnosis of AKI; IQR, interquartile range (quartile 1, quartile 3); SD, standard deviation.

presence of AKI was consistent across each of the three studies (KDIGO stage 2 or 3). Similarly, the threshold used to define a positive test was consistent in all included studies [(TIMP-2) × (IGFBP-7) = 0.3]. Diagnostic accuracy summaries for the included studies are shown in *Table 13*.

Figure 3 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for Nephrocheck in the critical care unit using patient urine samples. The pooled sensitivity estimate was 0.90 (95% CI 0.85 to 0.93) and the pooled specificity estimate was 0.49 (95% CI 0.46 to 0.53). *Figure 4* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. The prediction and confidence regions are small, suggesting limited heterogeneity. This is to be expected given the highly controlled similarity in these studies.

Cardiac surgery: urine

One study including 50 patients [26 patients (52.0%) with a diagnosis of AKI and 24 patients (48.0%) without a diagnosis AKI] was identified for the use of Nephrocheck in the cardiac surgery setting using urine samples.[54] A summary of the baseline characteristics and test parameters for the included study is shown in *Table 14*. The outcome used to define a diagnosis of AKI was a RIFLE classification of ≥ R within 72 hours of surgery. The threshold used to define a positive test was whether the maximum (TIMP-2) × (IGFBP-7) value in the 24 hours post cardiopulmonary bypass (CPB) was > 0.3. A diagnostic accuracy summary for the included study is shown in *Table 15*. No meta-analysis was performed for this single study.

TABLE 13 Diagnostic accuracy summaries for studies included in meta-analysis for Nephrocheck in the critical care unit health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Kashani 2013[45]	90	313	11	314	0.891 (0.815 to 0.938)	0.501 (0.462 to 0.540)	1.785 (1.609 to 1.980)	0.217 (0.124 to 0.382)	8.21 (4.305 to 15.7)
Bihorac 2014[33]	65	182	6	155	0.915 (0.828 to 0.961)	0.460 (0.407 to 0.513)	1.695 (1.502 to 1.914)	0.184 (0.085 to 0.399)	9.21 (3.891 to 21.9)
Hoste 2014[44]	24	59	3	67	0.889 (0.719 to 0.961)	0.532 (0.445 to 0.617)	1.898 (1.510 to 2.387)	0.209 (0.071 to 0.615)	9.09 (2.602 to 31.7)

FIGURE 3 Forest plot for studies included in the meta-analysis and pooled estimates for sensitivity and specificity Nephrocheck in the critical care unit health-care setting using urine.

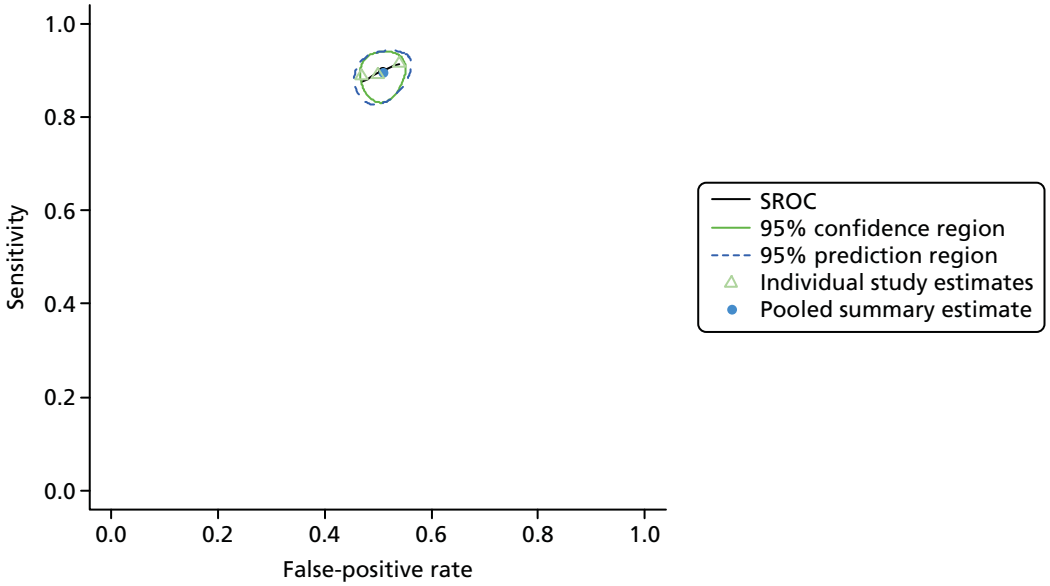

FIGURE 4 Summary receiver operating characteristic curve for studies included in the meta-analysis for Nephrocheck in the critical care unit health-care setting using urine.

TABLE 14 Characteristics of the study included for Nephrocheck in the cardiac surgery health-care setting using urine

First author and year	Patient group	Age (years)	Timing of test sample	Threshold	Outcome	Outcome	
						+	–
Meersch 2014[54]	Patients undergoing CPB	Mean (SD): ± 72 (11)	Maximum (TIMP-2) × (IGFBP7) in 24 hours post CPB	0.3	RIFLE (≥ R) within 72 hours of surgery	26	24

+, with a diagnosis of AKI; –, without a diagnosis of AKI; SD, standard deviation.

TABLE 15 Diagnostic accuracy summary for the study included for Nephrocheck in the cardiac surgery health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Meersch 2014[54]	24	8	2	16	0.923 (0.759 to 0.979)	0.667 (0.467 to 0.820)	2.769 (1.556 to 4.929)	0.115 (0.030 to 0.450)	24.00 (4.502 to 128.0)

Neutrophil gelatinase-associated lipocalin

Critical care unit: plasma

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 16*. Eight studies were included,[35,43,48,49,51,59,66,100] with a total of 1670 patients [381 patients (22.8%) with a diagnosis of AKI and 1289 patients (77.2%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies, with six studies[35,43,49,59,66,100] using a diagnostic outcome and two studies[48,51] using a failure-type outcome. There was also heterogeneity in the time at which the outcome assessment occurred (unclear, 48 hours and 7 days). Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 242 pg/ml[49] to 558 ng/ml.[43] Diagnostic accuracy summaries for the included studies are provided in *Table 17*.

TABLE 16 Characteristics of studies included in meta-analysis for NGAL in the critical care unit health-care setting using plasma

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)[a]	Outcome	Outcome	
						+	–
Constantin 2010[36]	Patients admitted to the critical care unit	Mean (SD): ± 57 (16)	Within 2 hours of admission	303	RIFLE (≥ R) within 7 days of admission	7	81
de Geus 2011[100]	Patients admitted to the critical care unit	Median (IQR): + 62 (50, 68); – 58 (43, 68)	On admission	417	RIFLE (≥ F) within 7 days of admission	56	461
Kokkoris 2012[48]	Patients admitted to the critical care unit	Median (IQR): + 63 (50.3, 80.8); – 49 (35.0, 66.3)	Within 13 hours of admission	62	RIFLE (≥ R) within 7 days of admission	36	64
Linko 2013[51]	Critically ill patients receiving ventilator support	Median (SD): ± 61 (51, 73)	Enrolment (at least 6 hours' ventilator support)	304	RRT (AKIN 3, KDIGO 3)	87	282
Hjortrup 2015[43]	Patients admitted to the critical care unit with severe sepsis and in need of fluid resuscitation	Median (IQR): ± 66 (63, 85)	Enrolment	558	KDIGO (≥ 1) within 48 hours of enrolment	31	100
Legrand 2015[49]	Patients admitted to the critical care unit with oliguria (diuresis < 0.5 ml/hour/kg for > 6 consecutive hours)	Median (IQR): + 55 (41, 70); – 55 (41, 70)	At time of oliguria diagnosis	242 pg/ml	KDIGO (≥ 1) within 7 days of admission	41	70
Palazzuoli 2015[59]	Acute heart failure (evidence of volume overload, pulmonary congestion or BNP greater than the ULN for age)	Mean (SD): + 78 (9); – 80 (8)	Within 24 hours of admission	134	AKIN (≥ 1) during the hospitalisation period	78	125
Shum 2015[66]	Patients admitted to the critical care unit and expected to stay for > 24 hours	Median (IQR): + 74 (60, 83); – 64 (54, 78)	6 hours after admission	230	AKIN (≥ 1) within 48 hours of admission	45	106

+, with a diagnosis of AKI; –, without a diagnosis of AKI; IQR, interquartile range (quartile 1, quartile 3); SD, standard deviation; ULN, upper-limit of normal.
a Threshold measured in ng/ml unless stated otherwise.

TABLE 17 Diagnostic accuracy summaries for studies included in meta-analysis for NGAL in the critical care unit health-care setting using plasma

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Constantin 2010[36]	43	1	9	35	0.827 (0.703 to 0.906)	0.972 (0.858 to 0.995)	29.7 (4.29 to 206.4)	0.178 (0.098 to 0.323)	167.2 (20.20 to 1384)
de Geus 2011[100]	39	46	17	415	0.696 (0.567 to 0.801)	0.9 (0.869 to 0.924)	6.98 (5.04 to 9.65)	0.337 (0.227 to 0.502)	20.70 (10.85 to 39.49)
Kokkoris 2012[48]	26	14	10	50	0.722 (0.560 to 0.842)	0.781 (0.666 to 0.865)	3.302 (1.992 to 5.473)	0.356 (0.207 to 0.612)	9.286 (3.628 to 23.77)
Linko 2013[51]	59	73	28	209	0.678 (0.574 to 0.767)	0.741 (0.687 to 0.789)	2.62 (2.05 to 1.60)	0.434 (0.318 to 0.594)	6.033 (3.577 to 10.18)
Hjortrup 2015[43]	18	24	13	76	0.581 (0.408 to 0.736)	0.76 (0.668 to 0.833)	2.42 (1.53 to 3.83)	0.552 (0.359 to 0.847)	4.385 (1.877 to 10.24)
Legrand 2015[49]	33	14	8	56	0.805 (0.660 to 0.898)	0.8 (0.692 to 0.877)	4.024 (2.460 to 6.583)	0.244 (0.130 to 0.459)	16.50 (6.259 to 43.50)
Palazzuoli 2015[59]	66	25	12	100	0.846 (0.750 to 0.910)	0.8 (0.721 to 0.861)	4.231 (2.942 to 6.083)	0.192 (0.113 to 0.326)	22.00 (10.34 to 46.82)
Shum 2015[66]	26	25	19	81	0.578 (0.433 to 0.710)	0.764 (0.675 to 0.835)	2.45 (1.60 to 3.74)	0.553 (0.386 to 0.790)	4.434 (2.111 to 9.134)

Figure 5 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for NGAL in the critical care unit using patient plasma samples. The pooled sensitivity estimate was 0.72 (95% CI 0.65 to 0.79) and the pooled specificity estimate was 0.81 (95% CI 0.75 to 0.86). *Figure 6* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. The prediction interval shows that there is a degree of heterogeneity in sensitivity and specificity, probably reflecting the variability in outcome measures and cut-off points, as well as other unidentified sources of heterogeneity.

Critical care unit: serum

One study including 150 patients [43 patients (28.7%) with a diagnosis of AKI and 107 patients (71.3%) without a diagnosis of AKI] was identified for NGAL in the critical care unit setting using serum.[34] A summary of the baseline characteristics and test parameters for the included study is provided in *Table 18*. A diagnostic-type outcome was used to define the presence of AKI (AKIN stage 1 or above within 48 hours of admission). The threshold used to define a positive test was 110 ng/ml. A diagnostic accuracy summary for the included study is provided in *Table 19*. No meta-analysis was performed for this single study.

Critical care unit: urine

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 20*. Six studies were included,[32,34,35,43,48,100] with a total of 1194 patients [283 patients (23.7%) with a diagnosis of AKI and 911 patients (76.3%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies. Of the studies included, five had a similar end point,[32,34,35,43,48] being at least the least severe stage of the RIFLE, AKIN or KDIGO classification system. There was heterogeneity in the time up to which the outcome assessment occurred (from 28 hours up to the end of the hospital stay). Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 29.5 ng/ml[32] to 1310 ng/ml.[100] Diagnostic accuracy summaries for the included studies are shown in *Table 21*.

Study	Sensitivity (95% CI)	Specificity (95% CI)
Constantin *et al.* 2010[36]	0.83 (0.70 to 0.91)	0.97 (0.86 to 1.00)
de Geus *et al.* 2011[100]	0.70 (0.57 to 0.80)	0.90 (0.87 to 0.92)
Kokkoris *et al.* 2012[48]	0.72 (0.56 to 0.84)	0.78 (0.67 to 0.86)
Linko *et al.* 2013[51]	0.68 (0.57 to 0.77)	0.74 (0.69 to 0.79)
Hjortrup *et al.* 2015[43]	0.58 (0.41 to 0.74)	0.76 (0.67 to 0.83)
Legrand *et al.* 2015[49]	0.80 (0.66 to 0.90)	0.80 (0.69 to 0.88)
Palazzuoli *et al.* 2015[59]	0.85 (0.75 to 0.91)	0.80 (0.72 to 0.86)
Shum *et al.* 2015[66]	0.58 (0.43 to 0.71)	0.76 (0.67 to 0.83)
Summary	0.72 (0.65 to 0.79)	0.81 (0.75 to 0.86)

FIGURE 5 Forest plot for studies included in the meta-analysis and pooled estimates for NGAL in the critical care unit health-care setting using plasma.

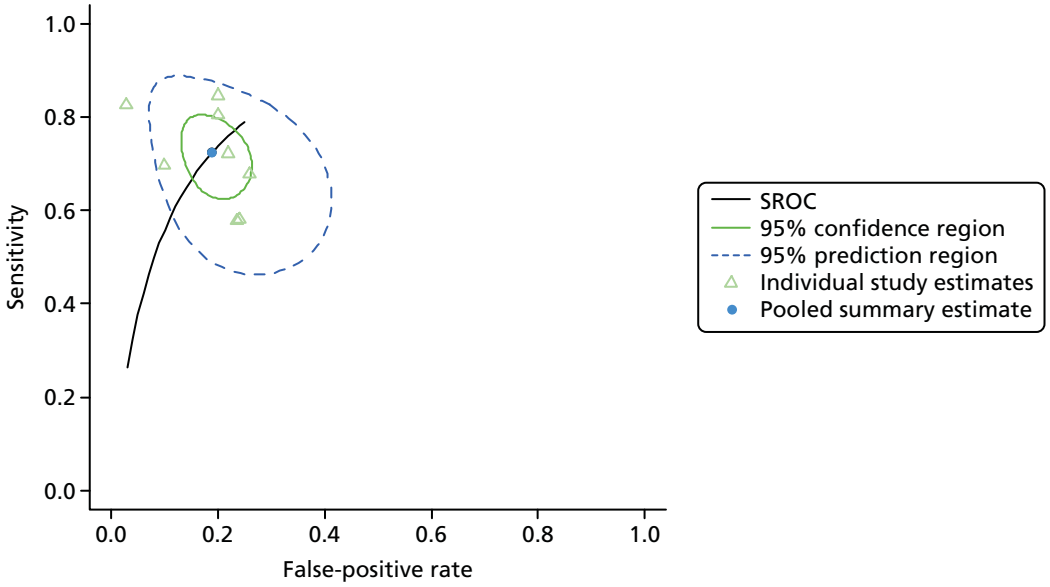

FIGURE 6 Summary receiver operating characteristic curve for studies included in the meta-analysis for NGAL in the critical care unit health-care setting using plasma.

TABLE 18 Characteristics of the study included for NGAL in the critical care unit health-care setting using serum

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Chen 2012[34]	Patients admitted to the critical care unit	Mean (SE): 66 (1)	Admission	110	AKIN (≥ 1) within 48 hours of admission	43	107

+, with a diagnosis of AKI; –, without a diagnosis of AKI; SE, standard error of the mean.

TABLE 19 Diagnostic accuracy summary for the study included for NGAL in the critical care unit health-care setting using serum

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Chen 2012[34]	39	4	33	74	0.542 (0.427 to 0.652)	0.949 (0.875 to 0.98)	10.562 (3.973 to 28.084)	0.483 (0.374 to 0.624)	21.864 (7.221 to 66.195)

Figure 7 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for NGAL in the critical care unit using patient urine samples. The pooled sensitivity estimate was 0.70 (95% CI 0.59 to 0.80) and the pooled specificity estimate was 0.79 (95% CI 0.71 to 0.86). *Figure 8* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. The prediction region shows that there is a degree of heterogeneity in sensitivity and specificity, probably reflecting the variability in outcome measures and cut-off points, as well as other unidentified sources of heterogeneity.

TABLE 20 Characteristics of studies included in meta-analysis for NGAL in the critical care unit health-care setting using urine

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
de Geus 2011[100]	Patients admitted to the critical care unit	Median (IQR): + 62 (50, 68); – 58 (43, 68)	On admission	1310	RIFLE (≥ F) within 7 days of admission	56	461
Chen 2012[34]	Patients admitted to the critical care unit	Mean (SE): 66 (1)	On admission	110	AKIN (≥ 1) within 48 hours of admission	43	107
Kokkoris 2012[48]	Patients admitted to the ICU	Median (IQR): + 63 (50.3, 80.8); – 49 (35.0, 66.3)	Within 13 hours of admission	58.5	RIFLE (≥ R) within 7 days of admission	36	64
Aydogdu 2013[32]	Patients admitted to the ICU (without previous history of renal disease)	Mean (SD): + 70 (13) (sepsis); – 66 (10) (no sepsis); – 67 (15) (sepsis)	Daily throughout hospital stay	29.5	RIFLE (≥ R) during hospital stay	63	88
Cho 2013[35]	Patients admitted to the medical or surgical ICU	Mean (SD): + 65.4 (14.8); – 60.4 (17.4)	On admission to the ICU	251	AKIN (≥ 1) within 5 days of admission	54	91
Hjortrup 2015[43]	Patients admitted to the critical care unit with severe sepsis and in need of fluid resuscitation	Median (IQR): ± 66 (63, 85)	Enrolment	558	KDIGO (≥ 1) within 48 hours of enrolment	31	100

+, with a diagnosis of AKI; –, without a diagnosis of AKI; IQR, interquartile range (quartile 1, quartile 3); SD, standard deviation; SE, standard error of the mean.

TABLE 21 Diagnostic accuracy summaries for studies included in meta-analysis for NGAL in the critical care unit health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
de Geus 2011[100]	31	46	25	415	0.554 (0.424 to 0.676)	0.900 (0.869 to 0.924)	5.55 (3.87 to 7.96)	0.496 (0.370 to 0.665)	11.2 (6.09 to 20.6)
Chen 2012[34]	28	17	15	90	0.651 (0.502 to 0.776)	0.841 (0.760 to 0.898)	4.098 (2.516 to 6.675)	0.415 (0.273 to 0.629)	9.882 (4.380 to 22.295)
Kokkoris 2012[34]	28	18	8	46	0.778 (0.619 to 0.883)	0.719 (0.599 to 0.814)	2.765 (1.801 to 4.246)	0.309 (0.165 to 0.581)	8.944 (3.438 to 23.271)
Aydogdu 2013[32]	55	24	8	64	0.873 (0.769 to 0.934)	0.727 (0.626 to 0.809)	3.201 (2.247 to 4.560)	0.175 (0.090 to 0.338)	18.333 (7.623 to 44.092)
Cho 2013[35]	40	27	14	64	0.741 (0.611 to 0.839)	0.703 (0.603 to 0.787)	2.497 (1.753 to 3.555)	0.369 (0.230 to 0.590)	6.772 (3.177 to 14.435)
Hjortrup 2015[43]	17	23	14	77	0.548 (0.378 to 0.708)	0.770 (0.678 to 0.842)	2.38 (1.48 to 3.85)	0.587 (0.392 to 0.877)	4.07 (1.74 to 9.48)

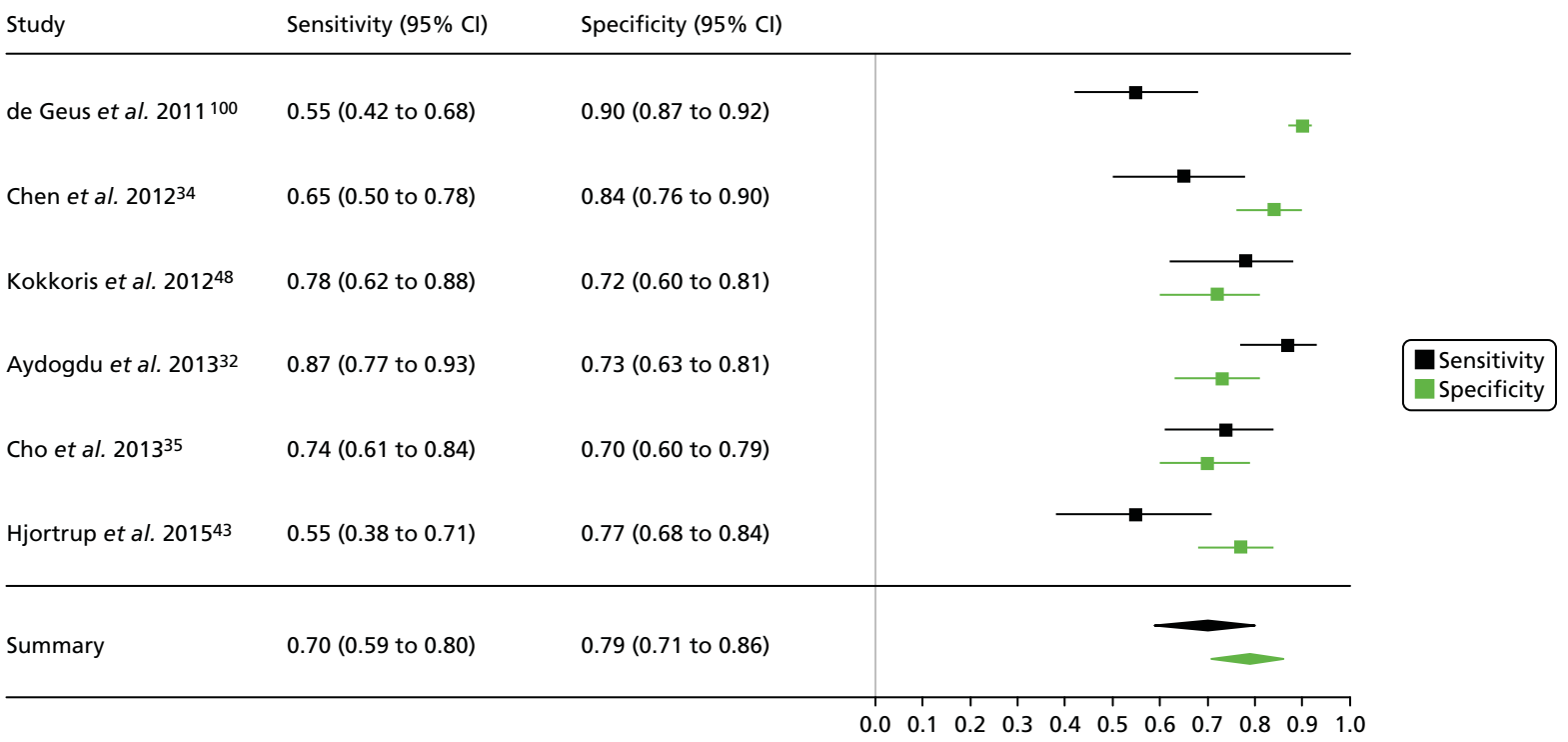

FIGURE 7 Forest plot for studies included in the meta-analysis and pooled estimates for NGAL in the critical care unit health-care setting using urine.

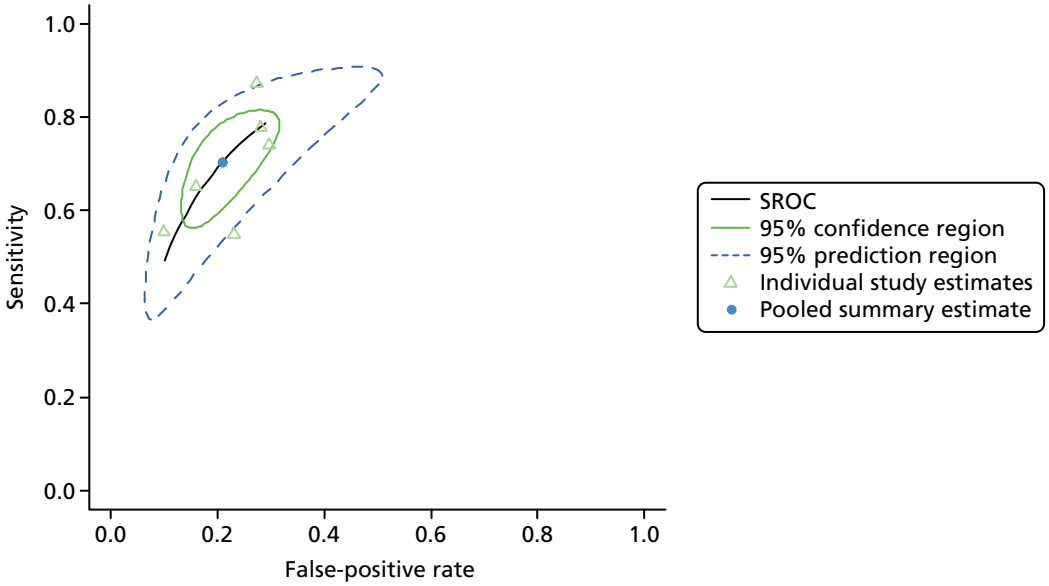

FIGURE 8 Summary receiver operating characteristic curve for studies included in the meta-analysis for NGAL in the critical care unit health-care setting using urine.

Cardiac surgery: plasma

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 22*. Eight studies were included,[31,40,47,60–63,67] with a total of 2644 patients [286 patients (10.8%) with a diagnosis of AKI and 2358 patients (89.2%) without a diagnosis of AKI]. The outcome used to define a diagnosis of AKI was largely consistent across the studies, although there was some heterogeneity in the time period in which the outcome was assessed. However, one study, used an end point that could not easily be mapped to the considered criteria.[67] Each of these could be considered to be somewhere between the least two severe categories of the RIFLE, AKN or KDIGO classification system. Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 150 ng/ml[31] to 426 ng/ml.[67] Diagnostic accuracy summaries for the included studies are shown in *Table 23*.

Figure 9 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for NGAL in the cardiac surgery setting using patient plasma samples. The pooled sensitivity estimate was 0.62 (95% CI 0.49 to 0.74) and the pooled specificity estimate was 0.78 (95% CI 0.75 to 0.81). *Figure 10* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. The prediction region suggests limited heterogeneity when considering specificity, with far greater heterogeneity when considering sensitivity, confirming the observations that can be made from the forest plot (see *Figure 9*).

Cardiac surgery: serum

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 24*. Two studies were included,[38,68] with a total of 239 patients [53 patients (22.2%) with a diagnosis of AKI and 186 patients (77.8%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies, with one study[38] using a less stringent version of the AKIN stage 1 classification without justification. Similarly, the threshold used to define a positive test was not consistent, being 0.62 ng/ml in one study[38] and 133.7 ng/ml in the other study.[68] Diagnostic accuracy summaries for the included studies are shown in *Table 25*.

TABLE 22 Characteristics of studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using plasma

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Haase 2009[31]	Patients undergoing cardiac surgery	Mean (SD): + 74.2 (6.9); – 68.3 (10.3)	6 hours post CPB surgery	150	AKIN (≥ 1) within 5 days of admission	46	54
Haase-Fielitz 2009[40]	Patients undergoing cardiac surgery with CPB	Mean (SD): + 75.9 (4.8); – 67.6 (9.9)	On arrival in the ICU (6 hours)	150	AKIN (≥ 1) within 5 days of admission	23	77
Tuladhar 2009[67]	Patients undergoing cardiac surgery	Median (IQR): + 70 (57–78); – 66 (41, 81)	2 hours post surgery	426	An increase in SCr in the postoperative period by > 0.5 mg/dl from baseline	9	41
Perry 2010[63]	Patients undergoing CABG surgery	Mean (SD): + 65 (12); – 65 (10)	At CPB	353.5	AKIN (≥ 1) within 4 days postoperatively	75	804
Parikh 2011[60]	Patients undergoing cardiac surgery (CABG or valve surgery)	Mean (SD): ± 71 (10)	Soon after arrival in the ICU	293	AKIN (≥ 2) within 4 days postoperatively	60	1159
Kidher 2014[47]	Patients undergoing aortic valve replacement	Mean (SD): ± 71 (9)	3 hours post surgery	150	RIFLE (≥ R) within 2 days postoperatively	16	37
Park 2015[61]	Patients undergoing cardiovascular surgery with CPB	Median (IQR): + 65 (50, 74); – 54 (40, 61)	On admission	168.5	RIFLE (≥ R) within 3 days postoperatively	5	72
Perrotti 2015[62]	Patients undergoing cardiac surgery	Mean (SD): ± 77 (6)	15 minutes after interruption of extracorporeal circulation	178	RIFLE (≥ R) within 2 days postoperatively	52	114

+, with a diagnosis of AKI; –, without a diagnosis of AKI; CABG, coronary artery bypass graft; IQR, interquartile range (quartile 1, quartile 3); SCr, serum creatinine; SD, standard deviation.

TABLE 23 Diagnostic accuracy summaries for studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using plasma

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Haase 2009[31]	34	14	12	40	0.739 (0.597 to 0.844)	0.741 (0.611 to 0.839)	2.851 (1.760 to 4.618)	0.352 (0.211 to 0.587)	8.095 (3.303 to 19.84)
Haase-Fielitz 2009[40]	18	17	5	60	0.783 (0.581 to 0.903)	0.779 (0.675 to 0.857)	3.545 (2.212 to 5.681)	0.279 (0.127 to 0.611)	12.706 (4.114 to 39.24)
Tuladhar 2009[67]	7	14	2	27	0.778 (0.453 to 0.937)	0.659 (0.505 to 0.784)	2.278 (1.314 to 3.948)	0.337 (0.097 to 1.168)	6.750 (1.235 to 36.91)
Perry 2010[63]	29	149	46	655	0.387 (0.285 to 0.500)	0.815 (0.786 to 0.840)	2.086 (1.515 to 2.873)	0.753 (0.627 to 0.904)	2.771 (1.685 to 4.558)
Parikh 2011[60]	28	220	32	939	0.467 (0.346 to 0.591)	0.810 (0.787 to 0.832)	2.458 (1.830 to 3.304)	0.658 (0.519 to 0.835)	3.735 (2.203 to 6.332)
Kidher 2014[47]	13	4	3	33	0.812 (0.570 to 0.934)	0.892 (0.753 to 0.957)	7.516 (2.892 to 19.53)	0.210 (0.075 to 0.587)	35.750 (7.013 to 182.23)
Park 2015[61]	4	8	1	64	0.800 (0.376 to 0.964)	0.889 (0.796 to 0.943)	7.200 (3.278 to 15.81)	0.225 (0.039 to 1.301)	32.000 (3.172 to 322.8)
Perrotti 2015[62]	28	33	24	81	0.538 (0.405 to 0.667)	0.711 (0.621 to 0.786)	1.860 (1.269 to 2.726)	0.650 (0.474 to 0.891)	2.864 (1.452 to 5.647)

Study	Sensitivity (95% CI)	Specificity (95% CI)
Haase-Fielitz *et al.* 2009[40]	0.78 (0.58 to 0.90)	0.78 (0.67 to 0.86)
Haase *et al.* 2009[31]	0.74 (0.60 to 0.84)	0.74 (0.61 to 0.84)
Tuladhar *et al.* 2009[67]	0.78 (0.45 to 0.94)	0.66 (0.51 to 0.78)
Perry *et al.* 2010[63]	0.39 (0.28 to 0.50)	0.81 (0.79 to 0.84)
Parikh *et al.* 2011[60]	0.47 (0.35 to 0.59)	0.81 (0.79 to 0.83)
Kidher *et al.* 2014[47]	0.81 (0.57 to 0.93)	0.89 (0.75 to 0.96)
Park *et al.* 2015[61]	0.80 (0.38 to 0.96)	0.89 (0.80 to 0.94)
Perrotti *et al.* 2015[62]	0.54 (0.41 to 0.67)	0.71 (0.62 to 0.79)
Summary	0.62 (0.49 to 0.74)	0.78 (0.75 to 0.81)

FIGURE 9 Forest plot for studies included in the meta-analysis and pooled estimates for NGAL in the cardiac surgery health-care setting using plasma.

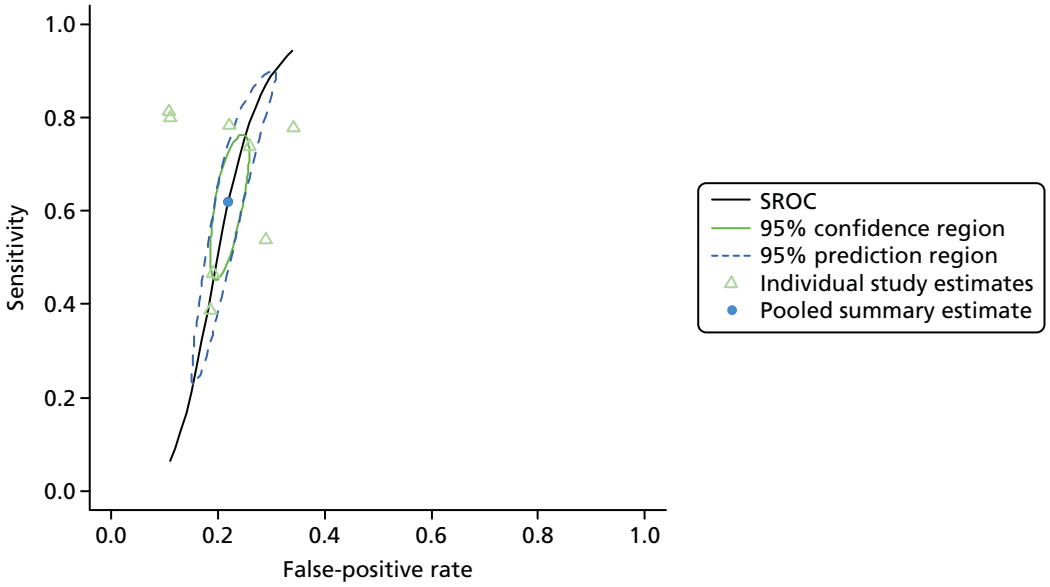

FIGURE 10 Summary receiver operating characteristic curve for studies included in the meta-analysis for NGAL in the cardiac surgery health-care setting using plasma.

TABLE 24 Characteristics of studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using serum

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Ghonemy 2014[38]	Patients undergoing CABG surgery or valve replacement	Range: + 39–56; – 32–53	3 hours postoperatively	0.62	An increase in SCr either by 25% of the baseline or by 0.3 mg/dl above the baseline level within 24 hours postoperatively	17	33
Tung 2015[68]	Patients with STEMI receiving PCI	Mean (SD): + 68.14 (12.6); – 61.33 (13.9)	At presentation	133.7	AKIN (≥ 1) within 48 hours of admission	36	153

+, with a diagnosis of AKI; –, without a diagnosis of AKI; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SCr, serum creatinine; SD, standard deviation; STEMI, ST elevation myocardial infarction.

TABLE 25 Diagnostic accuracy summaries for studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using serum

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Ghonemy 2014[38]	16	2	1	31	0.941 (0.730 to 0.990)	0.939 (0.804 to 0.983)	15.529 (4.032 to 59.81)	0.063 (0.009 to 0.420)	248.0 (20.87 to 2947)
Tung 2015[68]	25	35	11	118	0.694 (0.531 to 0.820)	0.771 (0.699 to 0.831)	3.036 (2.112 to 4.363)	0.396 (0.240 to 0.653)	7.66 (3.432 to 17.12)

Figure 11 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for NGAL in the cardiac surgery setting using patient serum samples. The pooled sensitivity estimate was 0.84 (95% CI 0.43 to 0.97) and the pooled specificity estimate was 0.87 (95% CI 0.59 to 0.97). *Figure 12* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. There appears to be considerable heterogeneity in both sensitivity and specificity.

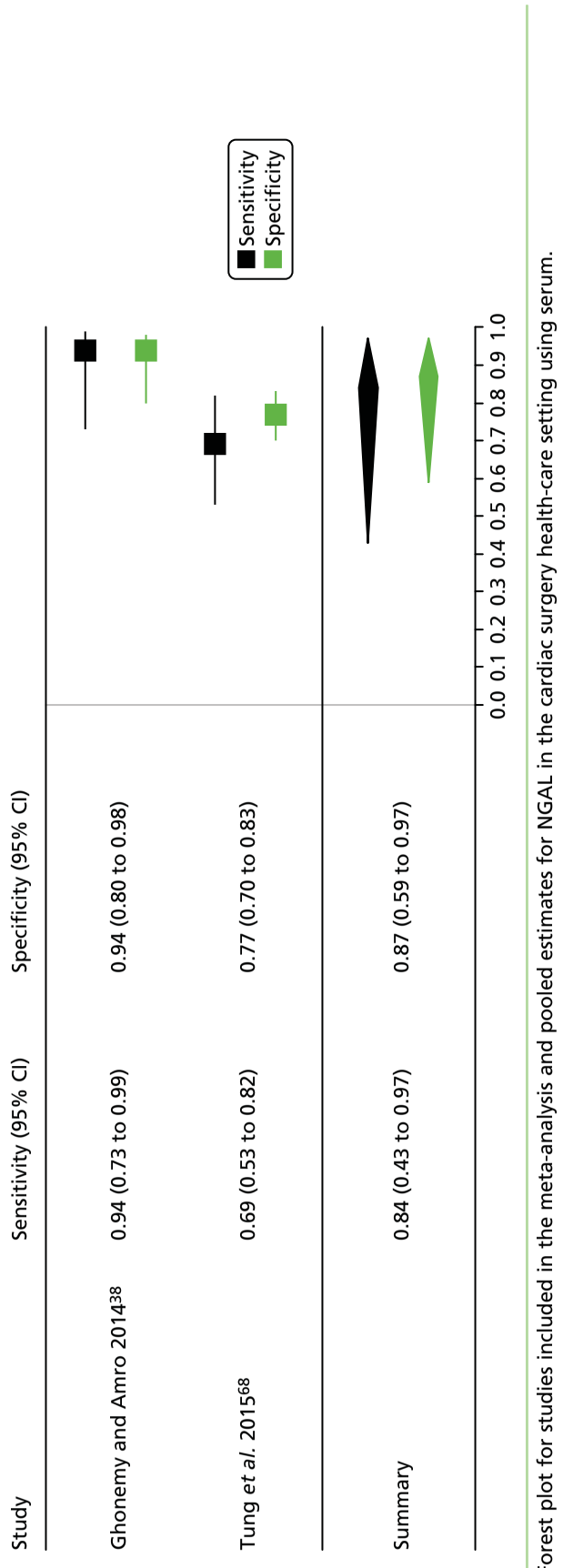

FIGURE 11 Forest plot for studies included in the meta-analysis and pooled estimates for NGAL in the cardiac surgery health-care setting using serum.

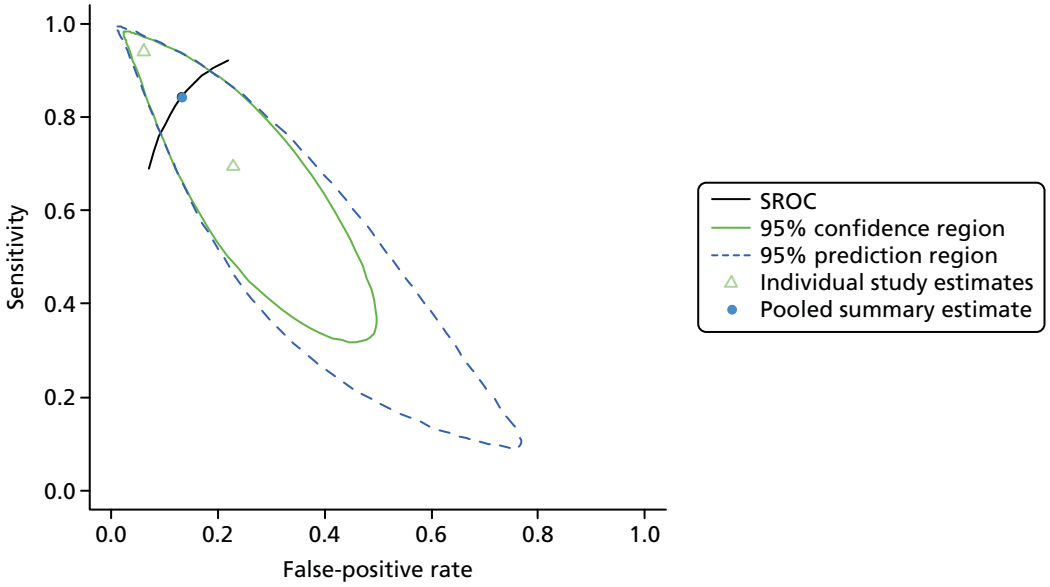

FIGURE 12 Summary receiver operating characteristic curve for studies included in the meta-analysis for NGAL in the cardiac surgery health-care setting using serum.

Cardiac surgery: urine

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 26*. Thirteen studies were included,[41,50,52,53,56,58,60,64,65,67,69,70,72] with a total of 3226 patients [444 patients (13.8%) with a diagnosis of AKI and 2782 patients (86.2%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was largely consistent across the studies, with one study[67] using a non-standard definition and one study[41] using only the serum creatinine assessment tool of the AKIN criteria. However, there was heterogeneity in the time to outcome assessment across the studies. The threshold used to define a positive test was not consistent across all of the studies, with some studies using raw concentration values and concentrations normalised by units of urine creatinine. Diagnostic accuracy summaries for the included studies are shown in *Table 27*.

TABLE 26 Characteristics of studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using urine

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)[a]	Outcome	Outcome	
						+	–
Wagener 2008[72]	Patients undergoing cardiovascular surgery	Mean (SD): + 69.5 (13.1); – 61.7 (14.9)	Immediately post surgery	23.5	AKIN (≥ 1) within 48 hours postoperatively	85	341
Han 2009[41]	Patients undergoing cardiovascular surgery	Mean (SD): + 68.3 (2.3); – 60.4 (1.98)	Immediately post surgery	456.0 ng/mg of creatinine	Modified AKIN stages 1 and 2 within 72 hours postoperatively[b]	36	54
Liangos 2009[50]	Patients undergoing on-pump cardiovascular surgery	Mean (SD): + 73 (9); – 67 (12)	2 hours post surgery	166 ng/mg of creatinine	RIFLE (≥ R) within 72 hours postoperatively	13	90

TABLE 26 Characteristics of studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using urine (*continued*)

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)[a]	Outcome	Outcome	
						+	–
Tuladhar 2009[67]	Patients undergoing cardiac surgery	Median (IQR): + 70 (57, 78); – 66 (41, 81)	2 hours post surgery	393 ng/mmol of creatinine	An increase in SCr in the postoperative period by > 0.5 mg/dl from baseline	9	41
McIlroy 2010[53]	Hospitalised patients undergoing contrast-enhanced CT	–	Immediately post surgery	8	AKIN (≥ 1) within 48 hours postoperatively	8	45
Parikh 2011[60]	Patients undergoing cardiac surgery (CABG or valve surgery)	Mean (SD): ± 71 (10)	Soon after arrival in the ICU	102	AKIN (≥ 2) within 4 days postoperatively	60	1159
Oh 2012[58]	Patients undergoing CABG surgery	Median (IQR): placebo: + 73 (69, 77.5), – 68 (62, 72); EPO: + 70 (62, 75), – 62 (56.5, 72.5)	Immediately post surgery	5	AKIN (≥ 1) within 72 hours postoperatively	21	50
Sargentini 2012[65]	Patients undergoing cardiovascular surgery	Mean (SD): + 74 (6); – 67 (11)	4 hours post ICU admission	55.2 mg/g of creatinine	AKIN (≥ 1) within 48 hours postoperatively	15	37
Liu 2013[52]	Patients undergoing cardiovascular surgery	Mean (SD): ± 63.0 (11.3)	Immediately postoperatively	131.1	AKIN (≥ 1) within 48 hours postoperatively excluding urine output	26	83
Munir 2013[56]	Patients undergoing cardiovascular surgery	Median (IQR): + 56 (47–64); – 51 (45–61)	4 hours post CPB	109	AKIN (≥ 1) within 48 hours postoperatively	11	77
Prowle 2015[64]	Patients undergoing cardiovascular surgery	Median (IQR): ± 70 (61–76)	Immediately postoperatively	195	RIFLE (≥ R) within 5 days postoperatively	25	68
Tziakas 2015[69]	Patients admitted with acute, spontaneous (type 1) AMI undergoing cardiovascular surgery	Mean (SD): ± 62 (13)	During admission	Unclear	AKIN (≥ 1) within 48 hours postoperatively	118	687
Varela 2015[70]	Patients undergoing cardiovascular surgery	Mean (SD): ± 68 (11)	6 hours	Unclear	AKIN (≥ 1) within 48 hours postoperatively	16	50

+, with a diagnosis of AKI; –, without a diagnosis of AKI; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CT, computerised tomography; EPO, erythropoietin; IQR, interquartile range (quartile 1, quartile 3); SCr, serum creatinine; SD, standard deviation.

a Threshold measured in ng/ml unless stated otherwise.

b Only absolute creatinine level used from stage 1 and all of stage 2 criterion.

TABLE 27 Diagnostic accuracy summaries for studies included in meta-analysis for NGAL in the cardiac surgery health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Wagener 2008[72]	26	65	59	276	0.306 (0.218 to 0.410)	0.809 (0.764 to 0.848)	1.605 (1.089 to 2.365)	0.858 (0.738 to 0.997)	1.871 (1.096 to 3.194)
Han 2009[41]	26	33	10	21	0.722 (0.560 to 0.842)	0.389 (0.270 to 0.522)	1.182 (0.881 to 1.585)	0.714 (0.383 to 1.333)	1.655 (0.665 to 4.117)
Liangos 2009[50]	9	80	4	10	0.692 (0.424 to 0.873)	0.111 (0.061 to 0.193)	0.779 (0.538 to 1.127)	2.769 (1.016 to 7.551)	0.281 (0.073 to 1.084)
Tuladhar 2009[67]	8	9	1	32	0.889 (0.565 to 0.980)	0.780 (0.633 to 0.880)	4.049 (2.175 to 7.540)	0.142 (0.022 to 0.910)	28.444 (3.131 to 258.4)
McIlroy 2010[53]	2	41	6	4	0.250 (0.071 to 0.591)	0.089 (0.035 to 0.207)	0.274 (0.082 to 0.914)	8.437 (3.051 to 23.34)	0.033 (0.005 to 0.218)
Parikh 2011[60]	30	209	30	950	0.500 (0.377 to 0.623)	0.820 (0.796 to 0.841)	2.773 (2.093 to 3.673)	0.610 (0.473 to 0.787)	4.545 (2.682 to 7.705)
Oh 2012[58]	19	26	2	24	0.905 (0.711 to 0.973)	0.480 (0.348 to 0.615)	1.740 (1.289 to 2.35)	0.198 (0.051 to 0.765)	8.769 (1.844 to 41.693)
Sargentini 2012[65]	8	10	7	27	0.533 (0.301 to 0.752)	0.730 (0.570 to 0.846)	1.973 (0.970 to 4.020)	0.640 (0.360 to 1.137)	3.086 (0.887 to 10.74)
Liu 2013[52]	20	15	6	68	0.769 (0.579 to 0.890)	0.819 (0.723 to 0.887)	4.256 (2.571 to 7.047)	0.282 (0.139 to 0.572)	15.111 (5.183 to 44.055)
Munir 2013[56]	6	1	5	76	0.545 (0.280 to 0.787)	0.987 (0.930 to 0.998)	42.000 (5.57 to 316. 8)	0.461 (0.241 to 0.880)	91.200 (9.123 to 911.7)
Prowle 2015[64]	19	27	6	41	0.760 (0.566 to 0.885)	0.603 (0.484 to 0.711)	1.914 (1.327 to 2.761)	0.398 (0.193 to 0.821)	4.809 (1.702 to 13.584)
Tziakas 2015[69]	14	17	2	33	0.875 (0.640 to 0.965)	0.660 (0.522 to 0.776)	2.574 (1.677 to 3.949)	0.189 (0.051 to 0.703)	13.588 (2.763 to 66.830)
Varela 2015[70]	89	378	30	309	0.748 (0.663 to 0.817)	0.450 (0.413 to 0.487)	1.359 (1.200 to 1.539)	0.560 (0.407 to 0.772)	2.425 (1.562 to 3.766)

Figure 13 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for NGAL in the cardiac surgery setting using patient urine samples. The pooled sensitivity estimate was 0.66 (95% CI 0.54 to 0.76) and the pooled specificity estimate was 0.62 (95% CI 0.41 to 0.79). *Figure 14* shows an estimate of the SROC with the 95% confidence region and 95% prediction region. The prediction interval covers almost all of the SROC space, suggesting that there is considerable heterogeneity between the studies included in this meta-analysis.

Cystatin C

Critical care unit: plasma

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 28*. Three studies were included,[32,48,49] with a total of 362 patients [140 patients (38.7%) with a diagnosis of AKI and 222 patients (61.3%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies. All of the studies can be considered to have used a similar end point, but there was heterogeneity in the time up to which the outcome assessment occurred (7 days post study entry up to during the hospital stay). Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 1040 ng/ml[48] to 1500 ng/ml.[32] Diagnostic accuracy summaries for the included studies are shown in *Table 29*.

Figure 15 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for cystatin C in the critical care unit using patient plasma samples. The pooled sensitivity

Study	Sensitivity (95% CI)	Specificity (95% CI)
Wagener *et al.* 2008[72]	0.31 (0.22 to 0.41)	0.81 (0.76 to 0.85)
Han *et al.* 2009[41]	0.72 (0.56 to 0.84)	0.39 (0.27 to 0.52)
Liangos *et al.* 2009[50]	0.69 (0.42 to 0.87)	0.11 (0.06 to 0.19)
Tuladhar *et al.* 2009[67]	0.89 (0.57 to 0.98)	0.78 (0.63 to 0.88)
McIlroy *et al.* 2010[53]	0.25 (0.07 to 0.59)	0.09 (0.04 to 0.21)
Parikh *et al.* 2011[60]	0.50 (0.38 to 0.62)	0.82 (0.80 to 0.84)
Oh *et al.* 2012[58]	0.90 (0.71 to 0.97)	0.48 (0.35 to 0.61)
Sargentini *et al.* 2012[65]	0.53 (0.30 to 0.75)	0.73 (0.57 to 0.85)
Liu *et al.* 2013[52]	0.77 (0.58 to 0.89)	0.82 (0.72 to 0.89)
Munir *et al.* 2013[56]	0.55 (0.28 to 0.79)	0.99 (0.93 to 1.00)
Prowle *et al.* 2015[64]	0.76 (0.57 to 0.89)	0.60 (0.48 to 0.71)
Tziakas *et al.* 2015[69]	0.75 (0.66 to 0.82)	0.45 (0.41 to 0.49)
Varela *et al.* 2015[70]	0.88 (0.64 to 0.97)	0.66 (0.52 to 0.78)
Summary	0.66 (0.54 to 0.76)	0.62 (0.41 to 0.79)

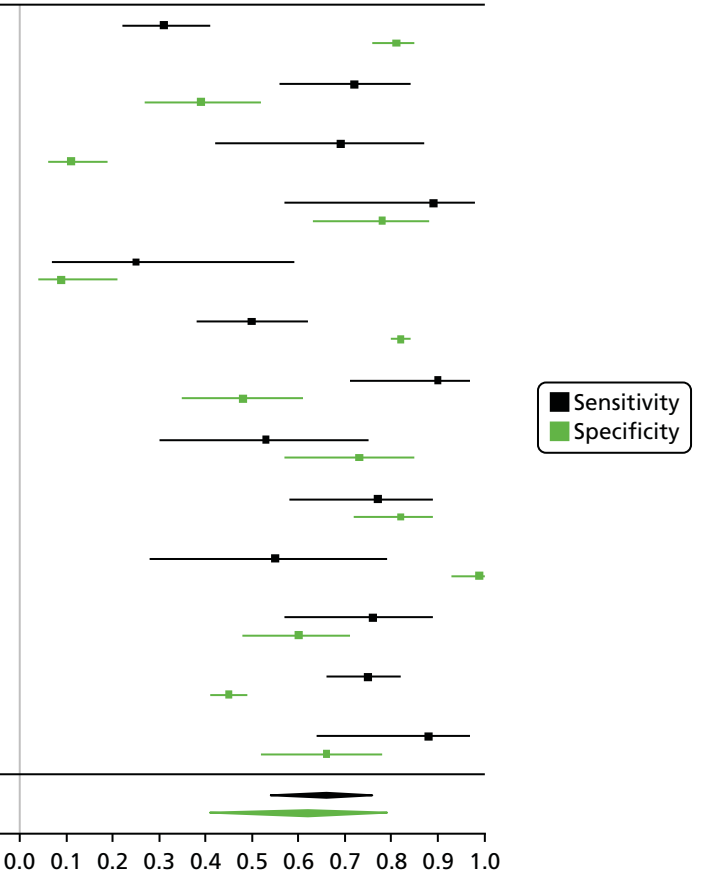

FIGURE 13 Forest plot for studies included in the meta-analysis and pooled estimates for NGAL in the cardiac surgery health-care setting using urine.

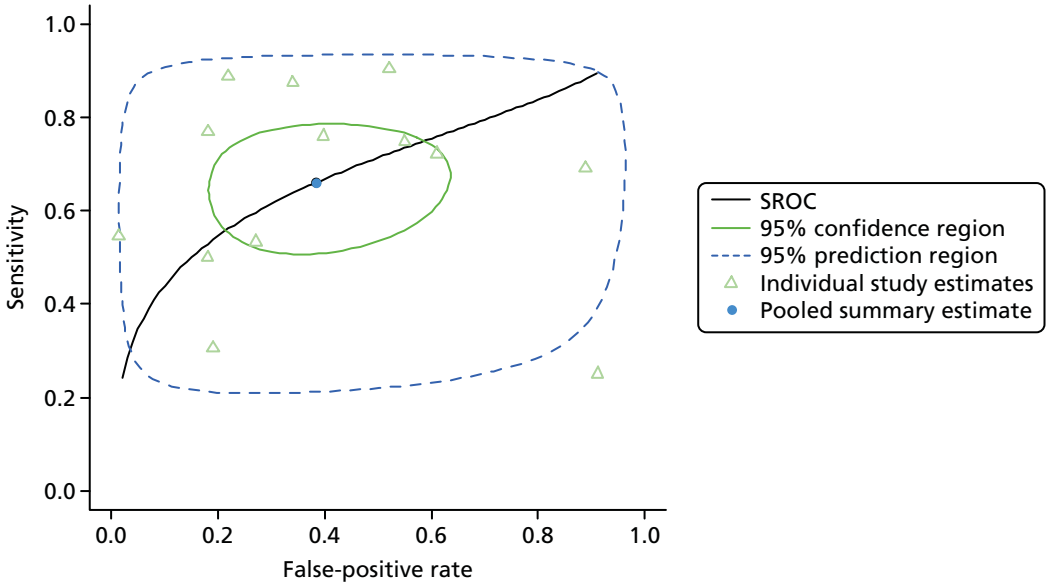

FIGURE 14 Summary receiver operating characteristic curve for studies included in the meta-analysis for NGAL in the cardiac surgery health-care setting using urine.

TABLE 28 Characteristics of studies included in meta-analysis for cystatin C in the critical care unit health-care setting using plasma

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Kokkoris 2012[48]	Patients admitted to the critical care unit	Median (IQR): + 63 (50.3, 80.8); – 49 (35.0, 66.3)	Within 13 hours of admission	1040	RIFLE (≥ R) within 7 days of admission	36	64
Aydogdu 2013[32]	Patients admitted to the ICU (without previous history of renal disease)	Mean (SD): + 70 (13) (sepsis); – 66 (10) (no sepsis); – 67 (15) (sepsis)	Daily throughout hospital stay	1500	RIFLE (≥ R) during the hospital stay	63	88
Legrand 2015[49]	Patients admitted to the critical care unit with oliguria (diuresis < 0.5 ml/hour/kg for > 6 consecutive hours)	Median (IQR): + 55 (41, 70); – 55 (41, 70)	At the time of oliguria diagnosis	1375	KDIGO (≥ 1) within 7 days of admission	41	70

+, with a diagnosis of AKI; –, without a diagnosis of AKI; IQR, interquartile range (quartile 1, quartile 3); SD, standard deviation.

TABLE 29 Diagnostic accuracy summaries for studies included in meta-analysis for cystatin C in the critical care unit health-care setting using plasma

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Kokkoris 2012[48]	22	12	14	52	0.611 (0.449 to 0.752)	0.812 (0.700 to 0.889)	3.259 (1.838 to 5.779)	0.479 (0.313 to 0.733)	6.810 (2.719 to 17.055)
Aydogdu 2013[32]	46	28	17	60	0.730 (0.610 to 0.824)	0.682 (0.579 to 0.770)	2.295 (1.632 to 3.226)	0.396 (0.257 to 0.609)	5.798 (2.838 to 11.848)
Legrand 2015[49]	34	19	7	51	0.829 (0.687 to 0.915)	0.729 (0.615 to 0.819)	3.055 (2.031 to 4.595)	0.234 (0.118 to 0.467)	13.038 (4.946 to 34.364)

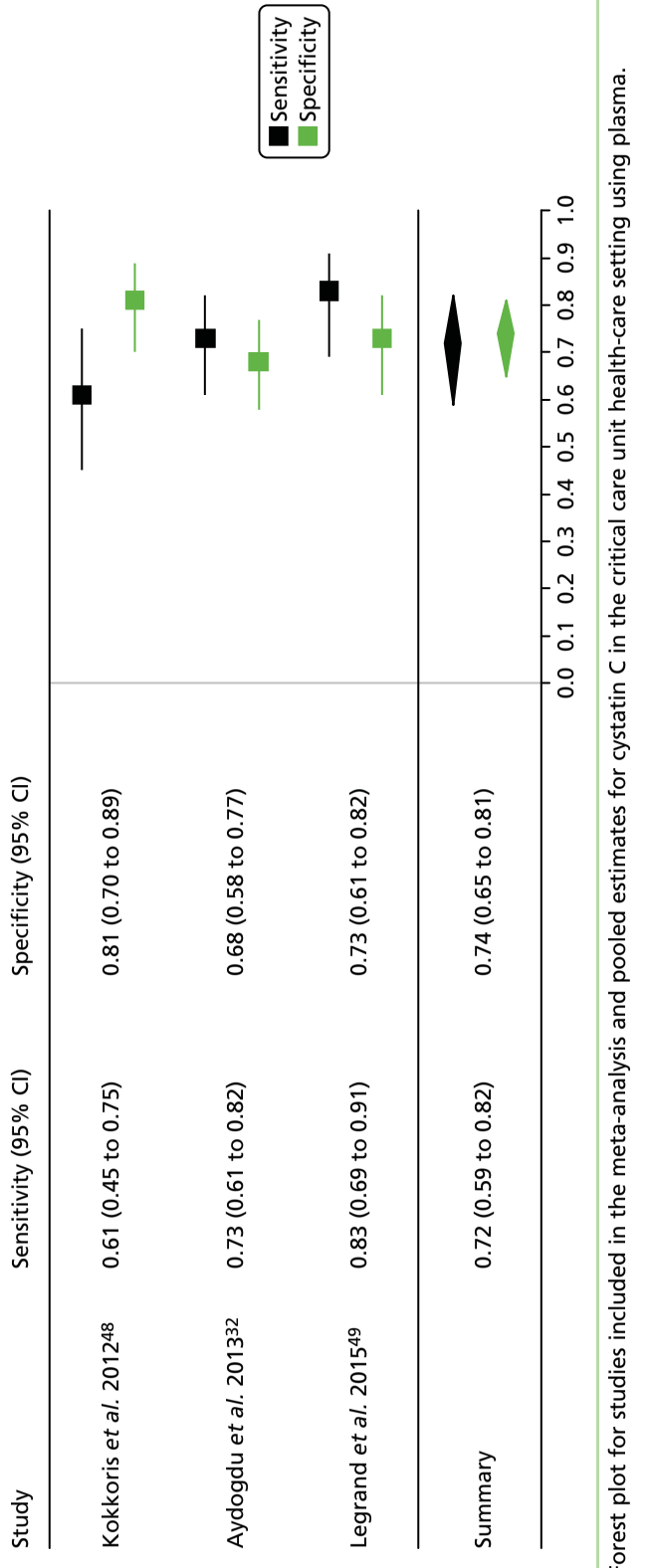

FIGURE 15 Forest plot for studies included in the meta-analysis and pooled estimates for cystatin C in the critical care unit health-care setting using plasma.

estimate was 0.72 (95% CI 0.59 to 0.82) and the pooled specificity estimate was 0.74 (95% CI 0.65 to 0.81). *Figure 16* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. Examining the forest plot and prediction region suggests that there is greater heterogeneity in sensitivity than in specificity.

Critical care unit: serum

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 30*. Four studies were included,[34,42,46,71] with a total of 372 patients [110 patients (29.6%) with a diagnosis of AKI

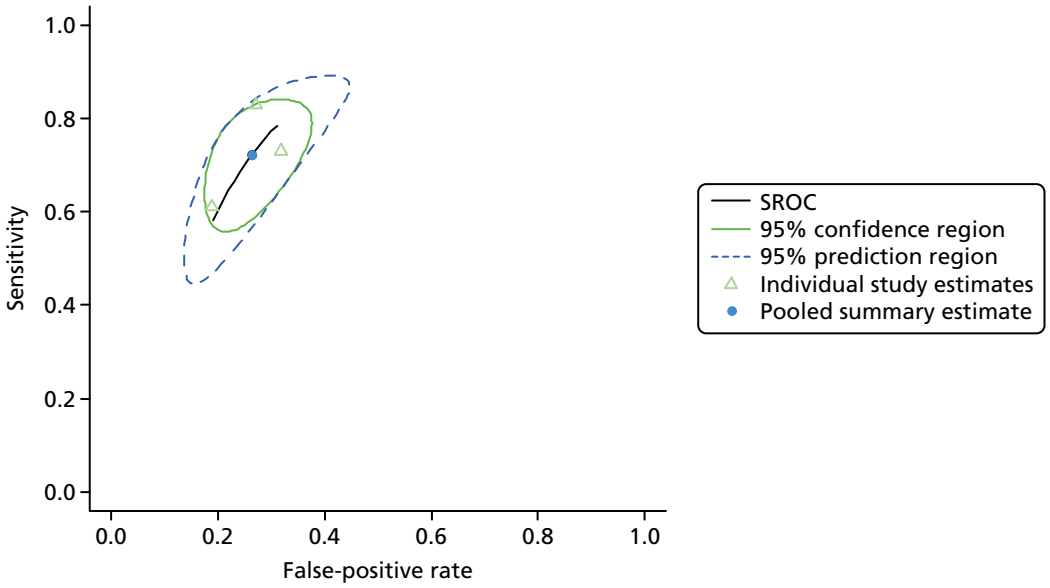

FIGURE 16 Summary receiver operating characteristic curve for studies included in the meta-analysis for cystatin C in the critical care unit health-care setting using plasma.

TABLE 30 Characteristics of studies included in meta-analysis for cystatin C in the critical care unit health-care setting using serum

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Herget-Rosenthal 2004[42]	Patients predisposed to acute renal failure in the critical care unit	Mean (SD): + 70 (8); – 63 (11)	On admission	–	RIFLE (≥ R) within 48 hours	24	61
Villa 2005[71]	Risk of renal failure	Range 21–86	In the morning	Elevated (no specific information)	Renal dysfunction (SCr < 80 ml/minute/1.73m^2 – based on 24-hour urine sample)	25	25
Kato 2008[46]	All patients scheduled for elective CAG returning to the critical care unit	Range 43–86	Prior to CAG	1200	An increase of > 25% from the baseline SCr value or an absolute increase of at least 0.5 mg/dl within 48 hours	18	69
Chen 2012[34]	Patients admitted to the critical care unit	Mean (SE): 66 (1)	On admission	1800	AKIN (≥ 1) within 48 hours of admission	43	107

+, with a diagnosis of AKI; –, without a diagnosis of AKI; CAG, coronary angiography; SCr, serum creatinine; SD, standard deviation; SE, standard error of the mean.

and 262 patients (70.4%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies, with one study using a definition that was less serious than the least serious stage of the RIFLE, AKIN or KDIGO classification system[46] and one study basing the outcome on continuous urine collection.[71] Similarly, the threshold used to define a positive test was not consistent across all of the studies, ranging from absolute values of 1200 ng/ml[46] to 1800 ng/ml[34] and with other patient-specific relative thresholds used. Diagnostic accuracy summaries for the included studies are shown in *Table 31*.

Figure 17 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for cystatin C in the critical care unit using patient serum samples. The pooled sensitivity estimate was 0.76 (95% CI 0.57 to 0.88) and the pooled specificity estimate was 0.91 (95% CI 0.85 to 0.95). *Figure 18* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region, which again shows greater heterogeneity in sensitivity than in specificity.

Critical care unit: urine

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 32*. Three studies were included,[32,34,175] with a total of 745 patients [231 patients (31.0%) with a diagnosis of AKI and 514 patients (69.0%) without a diagnosis of AKI]. The definition of AKI used was fairly consistent across the studies, but the time period within which the outcome was assessed varied from 48 hours to the entire length of the hospital stay. Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 106 ng/ml[32] to 200 ng/ml.[34] Diagnostic accuracy summaries for the included studies are shown in *Table 33*.

Figure 19 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for cystatin C in the critical care unit using patient urine samples. The pooled sensitivity estimate was 0.68 (95% CI 0.43 to 0.86) and the pooled specificity estimate was 0.76 (95% CI 0.62 to 0.86). *Figure 20* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. Heterogeneity appears to be considerable and greater in terms of sensitivity than specificity.

Cardiac surgery: plasma

The searches identified no studies suitable for data extraction for this diagnostic test, setting and sample type.

TABLE 31 Diagnostic accuracy summaries for studies included in meta-analysis for cystatin C in the critical care unit health-care setting using serum

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Herget-Rosenthal 2004[42]	13	3	11	58	0.542 (0.351 to 0.721)	0.951 (0.865 to 0.983)	11.014 (3.442 to 35.25)	0.482 (0.311 to 0.747)	22.848 (5.572 to 93.70)
Villa 2005[71]	19	2	6	23	0.760 (0.566 to 0.885)	0.920 (0.750 to 0.978)	9.500 (2.469 to 36.55)	0.261 (0.129 to 0.529)	36.417 (6.575 to 201.7)
Kato 2008[46]	17	10	1	59	0.944 (0.742 to 0.990)	0.855 (0.753 to 0.919)	6.517 (3.634 to 11.69)	0.065 (0.010 to 0.438)	100.300 (11.976 to 840.0)
Chen 2012[34]	33	10	10	97	0.767 (0.623 to 0.868)	0.907 (0.836 to 0.948)	8.212 (4.450 to 15.15)	0.257 (0.149 to 0.443)	32.010 (12.239 to 83.72)

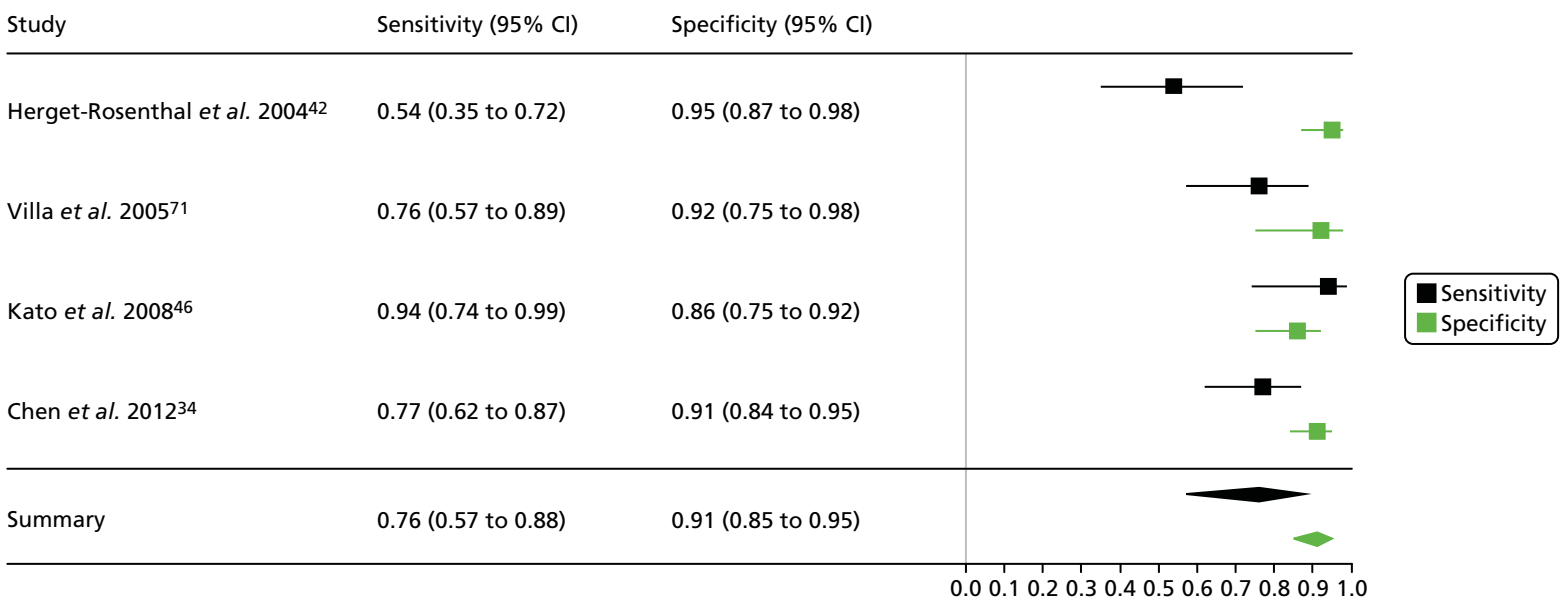

FIGURE 17 Forest plot for studies included in the meta-analysis and pooled estimates for cystatin C in the critical care unit health-care setting using serum.

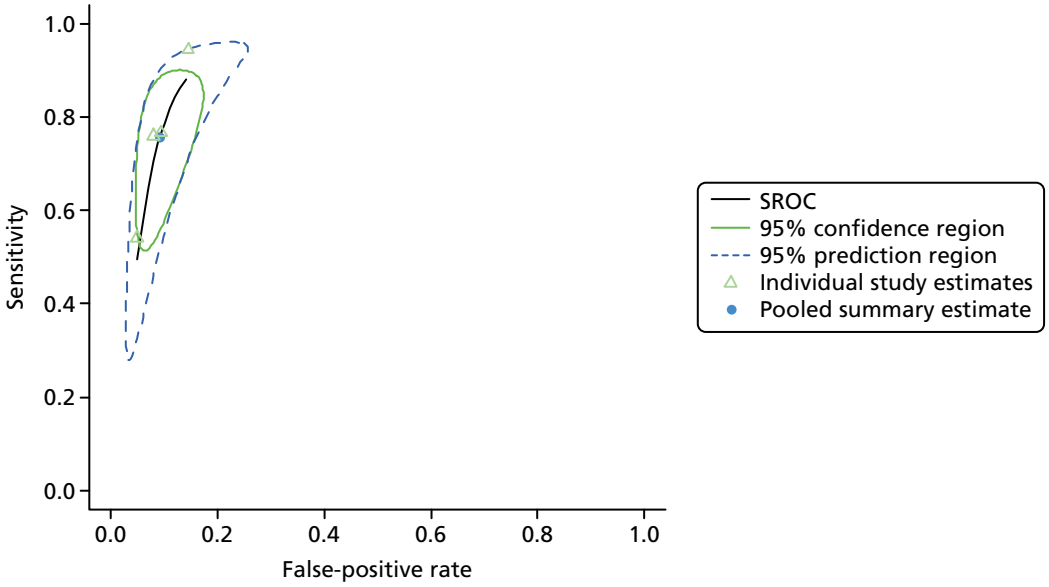

FIGURE 18 Summary receiver operating characteristic curve for studies included in the meta-analysis for cystatin C in the critical care unit health-care setting using serum.

TABLE 32 Characteristics of studies included in meta-analysis for cystatin C in the critical care unit health-care setting using urine

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Nejat 2010[175]	Patients admitted to the critical care unit	Mean (SD): + 62 (15); – 58 (18)	On admission	120	AKIN (≥ 1) within 7 days of admission	125	319
Chen 2012[34]	Patients admitted to the critical care unit	Mean (SE): 66 (1)	On admission	200	AKIN (≥ 1) within 48 hours of admission	43	107
Aydogdu 2013[32]	Patients admitted to the ICU (without a previous history of renal disease)	Mean (SD): + 70 (13) (sepsis); – 66 (10) (no sepsis); – 67 (15) (sepsis)	Daily throughout the hospital stay	106	RIFLE (≥ R) during the hospital stay	63	88

+, with a diagnosis of AKI; –, without a diagnosis of AKI; SD, standard deviation; SE, standard error of the mean.

TABLE 33 Diagnostic accuracy summaries for studies included in meta-analysis for cystatin C in the critical care unit health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Nejat 2010[175]	84	115	41	204	0.672 (0.586 to 0.748)	0.639 (0.585 to 0.690)	1.864 (1.540 to 2.256)	0.513 (0.394 to 0.668)	3.634 (2.346 to 5.631)
Chen 2012[34]	20	17	23	90	0.465 (0.325 to 0.611)	0.841 (0.760 to 0.898)	2.927 (1.704 to 5.029)	0.636 (0.476 to 0.850)	4.604 (2.085 to 10.17)
Aydogdu 2013[32]	54	18	9	70	0.857 (0.750 to 0.923)	0.795 (0.700 to 0.867)	4.190 (2.742 to 6.404)	0.180 (0.097 to 0.332)	23.333 (9.723 to 55.99)

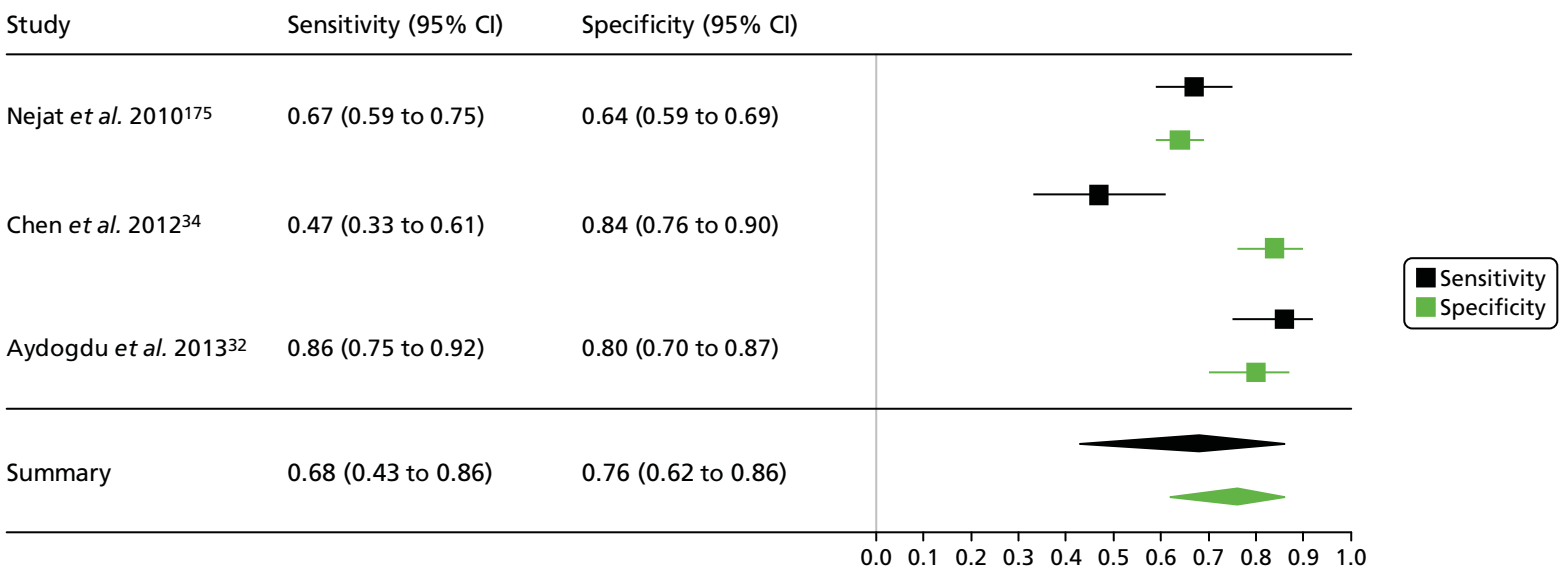

FIGURE 19 Forest plot for studies included in the meta-analysis and pooled estimates for cystatin C in the critical care unit health-care setting using urine.

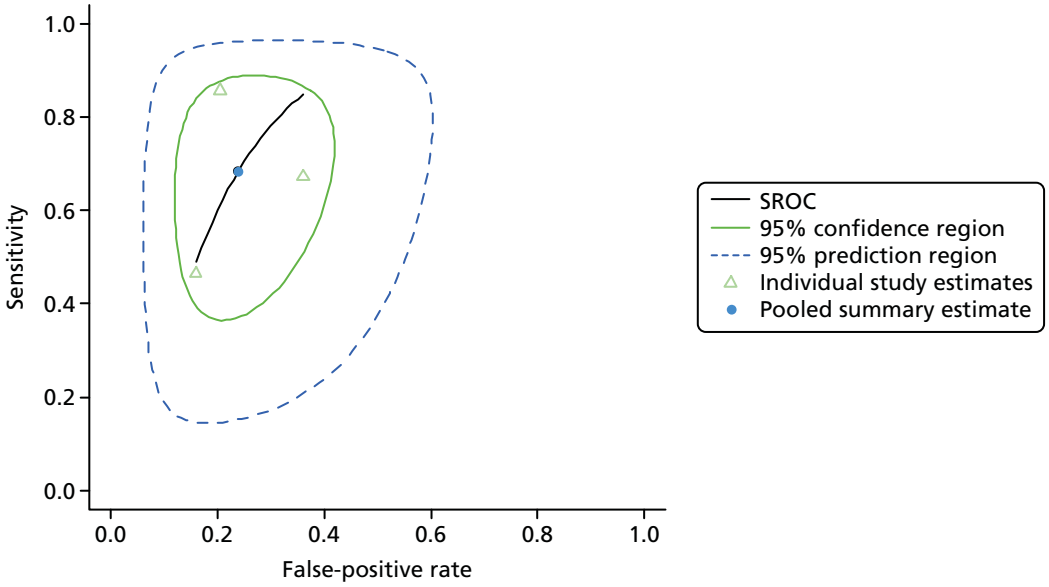

FIGURE 20 Summary receiver operating characteristic curve for studies included in the meta-analysis for cystatin C in the critical care unit health-care setting using urine.

Cardiac surgery: serum

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 34*. Five studies were included,[31,38,39,64,68] with a total of 532 patients [147 patients (27.6%) with a diagnosis of AKI and 385 patients (72.4%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was not consistent across the studies, with one study[38] using a definition that was less serious than the least serious stage of the RIFLE, AKIN or KDIGO classification system[17] and one study basing the outcome on continuous urine collection (from 48 hours up to 4 days post study entry). Similarly, the threshold used to define a positive test was not consistent across the studies, ranging from 0.0265 ng/ml (26.5 pg/ml) to 1100 ng/ml. Diagnostic accuracy summaries for the included studies are shown in *Table 35*.

Figure 21 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for cystatin C in the cardiac surgery setting using patient serum samples. The pooled sensitivity estimate was 0.73 (95% CI 0.65 to 0.80) and the pooled specificity estimate was 0.72 (95% CI 0.63 to 0.79). *Figure 22* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. The studies show limited evidence of heterogeneity, with a greater degree of heterogeneity with respect to specificity than sensitivity.

Cardiac surgery: urine

Summaries of the baseline characteristics and test parameters for the included studies are shown in *Table 36*. Two studies were included,[50,69] with a total of 908 patients [131 patients (14.4%) with a diagnosis of AKI and 777 patients (85.6%) without a diagnosis of AKI]. The outcome used to define the presence of AKI was similar in both studies, although the time frame over which the outcome was assessed varied by 24 hours. The threshold used to define a positive test was not consistent across the studies, with one study[69] not clearly reporting the threshold used. Diagnostic accuracy summaries for the included studies are shown in *Table 37*.

Figure 23 shows point estimates of the sensitivity and specificity from individual studies and the pooled estimates for cystatin C in the cardiac surgery setting using patient serum samples. The pooled sensitivity estimate was 0.52 (95% CI 0.27 to 0.76) and the pooled specificity estimate was 0.72 (95% CI 0.36 to 0.92). *Figure 24* shows an estimate of the SROC curve with the 95% confidence region and 95% prediction region. Examining the forest plot and prediction region in the SROC curve suggests that there is considerable heterogeneity between the studies in terms of sensitivity and specificity.

TABLE 34 Characteristics of studies included in meta-analysis for cystatin C in the cardiac surgery health-care setting using serum

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Haase 2009[31]	Patients undergoing cardiac surgery in a tertiary hospital	Mean (SD): + 74.2 (6.9); – 68.3 (10.3)	On arrival in the ICU (6 hours)	1.1	AKIN (≥ 1) within 5 days of admission	46	54
Haase-Fielitz 2009[39]	Patients undergoing cardiac surgery with CPB	Mean (SD): + 75.9 (4.8); – 67.6 (9.9)	On arrival in the ICU (6 hours)	1100	AKIN (≥ 1) within 5 days of admission	23	77
Ghonemy 2014[38]	Patients undergoing CABG surgery or valve replacement	Range: + 39–56; – 32–53	3 hours postoperatively	0.0265	An increase in SCr either by 25% of the baseline value or by 0.3 mg/dl above the baseline level within 24 hours postoperatively	17	33
Prowle 2015[64]	Patients undergoing cardiovascular surgery	Median (IQR): ± 70 (61–76)	Immediately postoperatively	1.24	RIFLE (≥ R) within 5 days postoperatively	25	68
Tung 2015[68]	Patients with STEMI receiving PCI	Mean (SD): + 68.14 (12.6); – 61.33 (13.9)	At presentation	1.6	AKIN (≥ 1) within 48 hours of admission	36	153

+, with a diagnosis of AKI; –, without a diagnosis of AKI; CABG, coronary artery bypass graft; IQR, interquartile range (quartile 1, quartile 3); PCI, percutaneous coronary intervention; SCr, serum creatinine; SD, standard deviation; STEMI, ST elevation myocardial infarction.

TABLE 35 Diagnostic accuracy summaries for studies included in meta-analysis for cystatin C in the cardiac surgery health-care setting using serum

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Haase 2009[31]	34	18	12	36	0.739 (0.597 to 0.844)	0.667 (0.534 to 0.778)	2.217 (1.465 to 3.356)	0.391 (0.232 to 0.659)	5.667 (2.379 to 13.50)
Haase-Fielitz 2009[39]	18	11	5	66	0.783 (0.581 to 0.903)	0.857 (0.762 to 0.918)	5.478 (3.043 to 9.863)	0.254 (0.116 to 0.554)	21.600 (6.646 to 70.20)
Ghonemy 2014[38]	9	9	8	24	0.529 (0.310 to 0.738)	0.727 (0.558 to 0.849)	1.941 (0.950 to 3.968)	0.647 (0.375 to 1.117)	3.000 (0.884 to 10.18)
Prowle 2015[64]	19	25	6	43	0.760 (0.566 to 0.885)	0.632 (0.514 to 0.737)	2.067 (1.411 to 3.028)	0.380 (0.185 to 0.780)	5.447 (1.922 to 15.44)
Tung 2015[68]	28	47	8	106	0.778 (0.619 to 0.883)	0.693 (0.616 to 0.760)	2.532 (1.885 to 3.401)	0.321 (0.173 to 0.596)	7.894 (3.349 to 18.61)

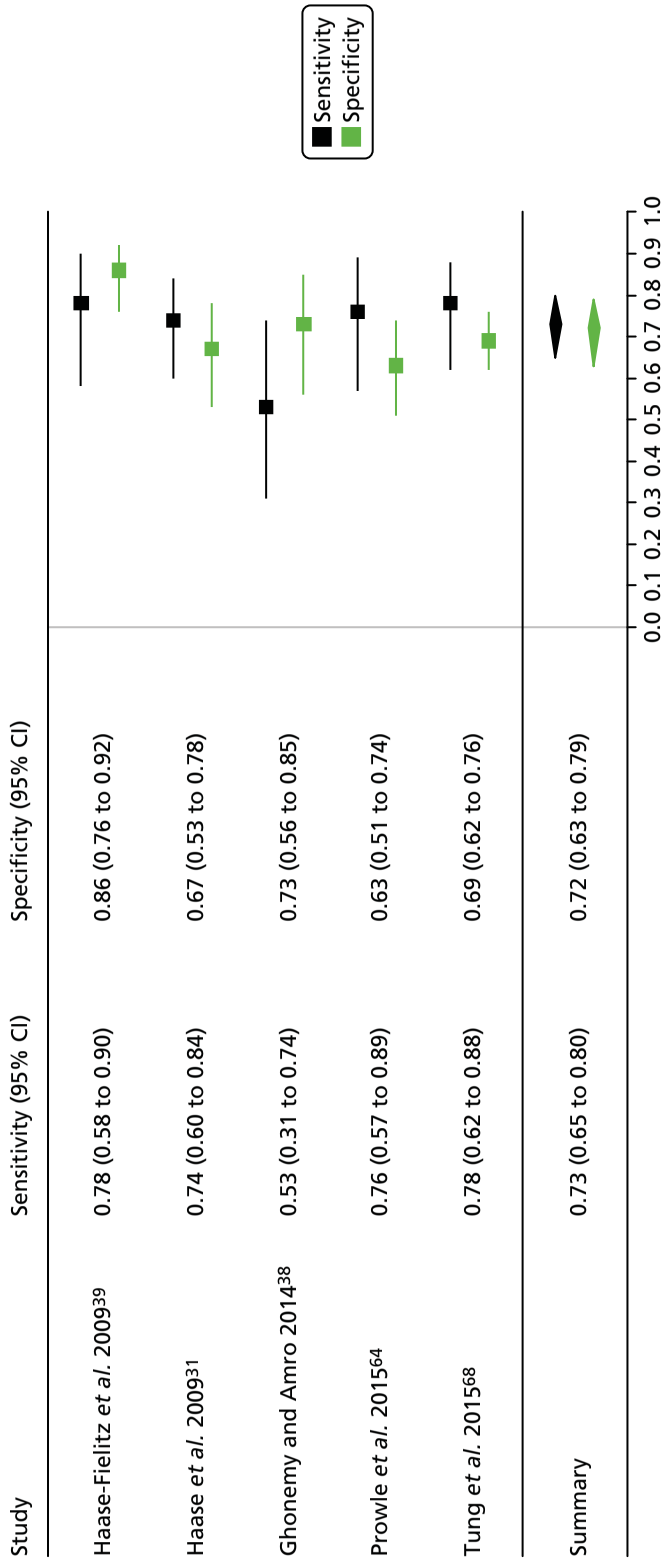

FIGURE 21 Forest plot for studies included in the meta-analysis and pooled estimates for cystatin C in the cardiac surgery health-care setting using serum.

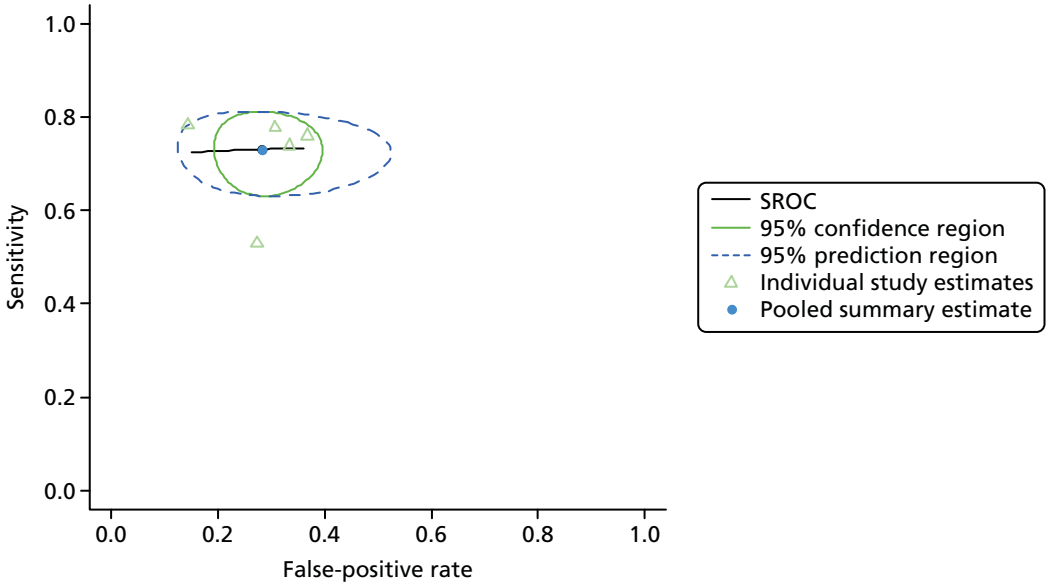

FIGURE 22 Summary receiver operating characteristic curve for studies included in the meta-analysis for cystatin C in the cardiac surgery health-care setting using serum.

TABLE 36 Characteristics of studies included in meta-analysis for cystatin C in the cardiac surgery health-care setting using urine

First author and year	Patient group	Age (years)	Timing of sample	Threshold (ng/ml)	Outcome	Outcome	
						+	–
Liangos 2009[50]	Patients undergoing on-pump cardiovascular surgery	Mean (SD): + 73 (9); – 67 (12)	2 hours post surgery	192 ng/mg of creatinine	RIFLE (≥ R) within 72 hours postoperatively	13	90
Tziakas 2015[69]	Patients admitted with spontaneous (type 1) AMI undergoing cardiovascular surgery	Mean (SD): ± 62 (13)	During admission	Unclear	AKIN (≥ 1) within 48 hours postoperatively	118	687

+, with a diagnosis of AKI; –, without a diagnosis of AKI; AMI, acute myocardial infarction; SD, standard deviation.

TABLE 37 Diagnostic accuracy summaries for studies included in meta-analysis for cystatin C in the cardiac surgery health-care setting using urine

First author and year	TP, *n*	FP, *n*	FN, *n*	TN, *n*	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)	DOR (95% CI)
Liangos 2009[50]	5	13	8	77	0.385 (0.177 to 0.645)	0.856 (0.768 to 0.914)	2.663 (1.136 to 6.241)	0.719 (0.464 to 1.115)	3.702 (1.047 to 13.083)
Tziakas 2015[69]	76	309	42	378	0.644 (0.554 to 0.725)	0.550 (0.513 to 0.587)	1.432 (1.223 to 1.676)	0.647 (0.503 to 0.832)	2.214 (1.475 to 3.321)

Limitations

A limitation of this work is the use of a number of similar criteria for diagnosing AKI based on the measurement of serum creatinine and urine output rather than a more direct and accurate determination of kidney function and injury. Criteria based on serum creatinine lack real-time sensitivity for kidney injury, as creatinine concentration has a slow rate of change and is affected by other factors such as sex and muscle mass. Current standard AKI criteria based on serum creatinine and urine output measures therefore

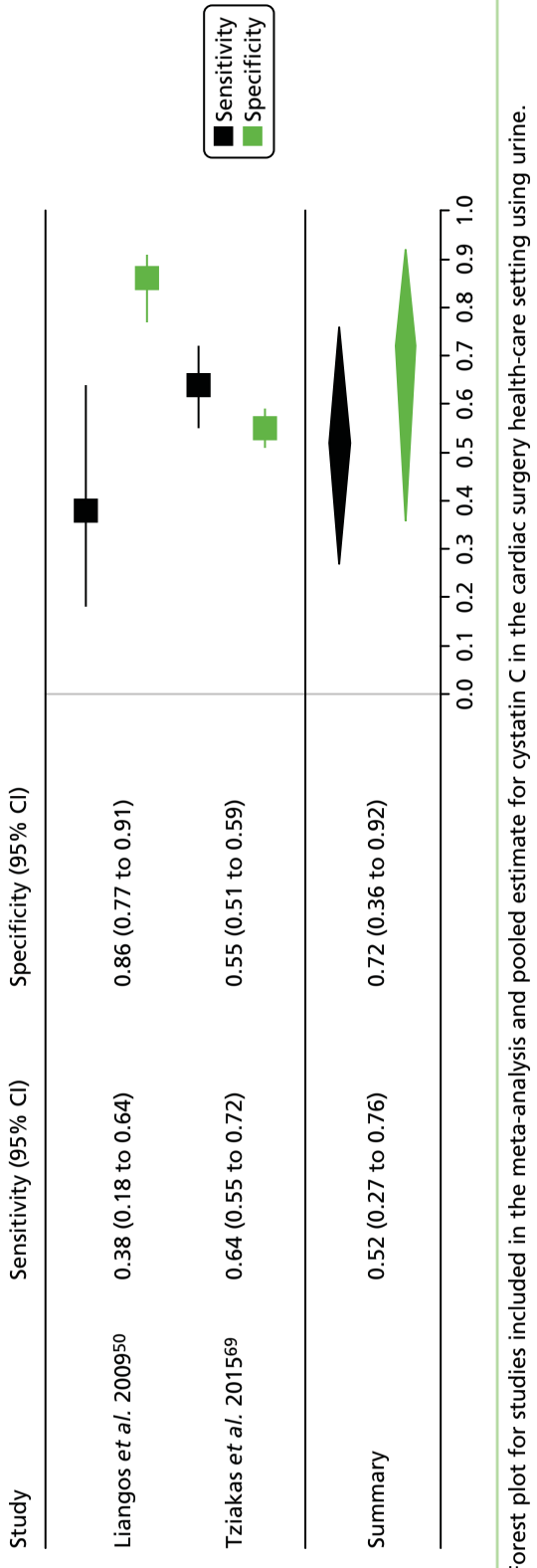

FIGURE 23 Forest plot for studies included in the meta-analysis and pooled estimate for cystatin C in the cardiac surgery health-care setting using urine.

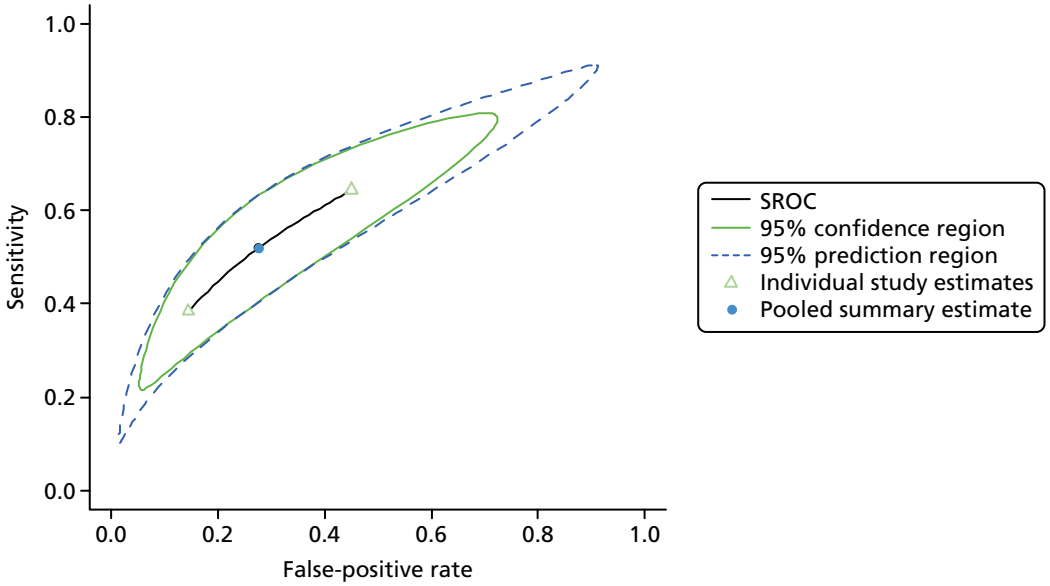

FIGURE 24 Summary receiver operating characteristic curve for studies included in the meta-analysis for cystatin C in the cardiac surgery health-care setting using urine.

represent an imperfect reference test for the early detection of AKI. Each of the studies considered in these meta-analyses used criteria based on changes in serum creatinine concentrations and is therefore affected equally by this limitation.

The method of meta-analysis used in this analysis is recommended by the Cochrane Screening and Diagnostic Tests Methods Group.[262] However, a similar method in the Bayesian paradigm, which has shown to be equivalent in simple cases, may have been a reasonable alternative.[259] Furthermore, this fully Bayesian approach has the advantage of potentially unifying the sensitivity analyses (assessment of uncertainty in the estimates in decision analysis) with the modelling step and of allowing predictions of test accuracies in future trials through a posterior predictive distribution. The hierarchical model approach may also have been flexible enough to include further modelling aspects related to analytical and biological variance of the diagnostic tests considered in this work, if enough studies were included to reasonably estimate models. This is not possible using the simple bivariate random-effects meta-analysis method and is a possible limitation of this work. Further work will consider in more detail the possibility of extending the hierarchical model to include these aspects and investigate if the hierarchical model can be estimated in meta-analyses of this size. Extension of this model that allows for imperfect gold reference standards may also be worthy of further investigation.[263]

There is evidence of considerable heterogeneity in some of the included studies, which is clearly observed in the large prediction regions in the SROC space. Two of the sources of heterogeneity are the outcome measures used and the time within which the outcome is assessed. As mentioned earlier, a limitation of this work is the use of criteria based on measurement of serum creatinine and urine output rather than a more direct determination of kidney function. If more studies had provided data, meta-regression may have been useful for isolating and quantifying some of these sources of heterogeneity further. Further investigations may be conducted into modelling these sources of heterogeneity as part of future work described above related to investigating the possible extension of the hierarchical regression models.

Summary

A number of the diagnostic tests for AKI considered in these meta-analyses may have a role to play in certain health-care settings and using particular sample media. The Nephrocheck test using urine in the critical care unit setting appears overall to have the best sensitivity, albeit with low specificity. The estimates of sensitivity are high and there is low heterogeneity. The NGAL test using plasma shows moderate sensitivity and high specificity, but greater heterogeneity. Other health-care settings and sample types show evidence of considerable heterogeneity between studies. Two studies that were included in previously published NGAL meta-analyses were excluded here as they included patients who originated in the emergency room and who were subsequently released to other hospital departments.[245,264]

Chapter 4 Measurement performance: a framework for the Quality Assessment of Measurement Procedures using in vitro diagnostic medical devices in clinical research

Introduction

It is generally accepted that between 60% and 80% of clinical decisions are influenced by the results of laboratory testing using IVDs.[265] A large proportion, although not all, of this testing is focused on the quantitative or semiquantitative measurement of biomarkers in patient samples. The accuracy and associated uncertainty of these measurements can have a major impact on the overall quality of clinical decisions and their subsequent clinical effectiveness and cost-effectiveness.[266,267]

The main factors affecting measurement uncertainty are shown in *Figure 25*. Laboratories and regulators have historically focused on analytical factors associated with the measurement system, including analytical imprecision and trueness (accuracy). However, it is increasingly accepted that the major sources of error (uncertainty) associated with biomarker measurements are derived from either the patients themselves or the acquisition of their samples, referred to respectively as biological and pre-analytical factors.[268,269] The uncertainty introduced by these factors accumulates throughout the measurement system, eventually affecting test performance, such as diagnostic accuracy (*Figure 26*).

Although there has been significant progress in characterising and controlling for measurement factors in clinical care, they are almost always poorly accounted for in clinical research.[271] This has led to recent criticisms and calls for more rigorous methodology in the field.[272]

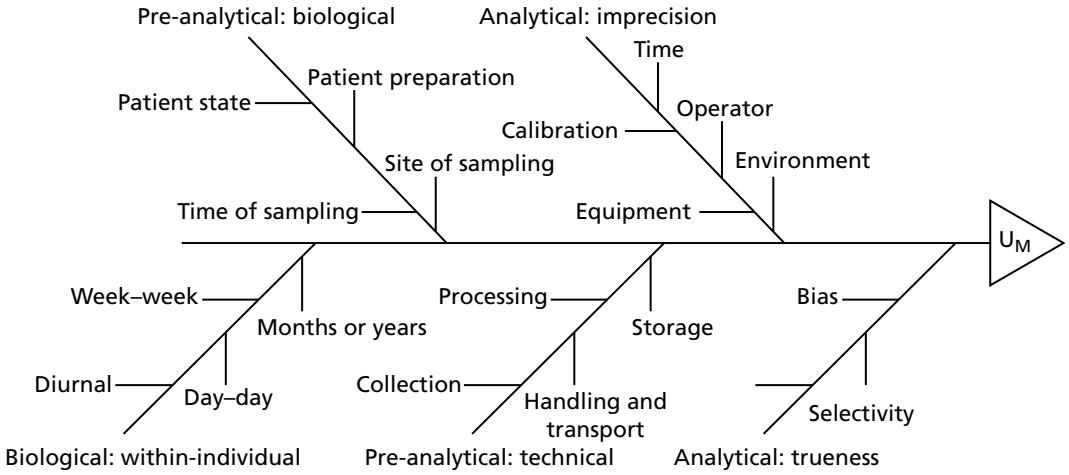

FIGURE 25 Feather diagram depicting sources of uncertainty contributing towards the measurement uncertainty (U_M).

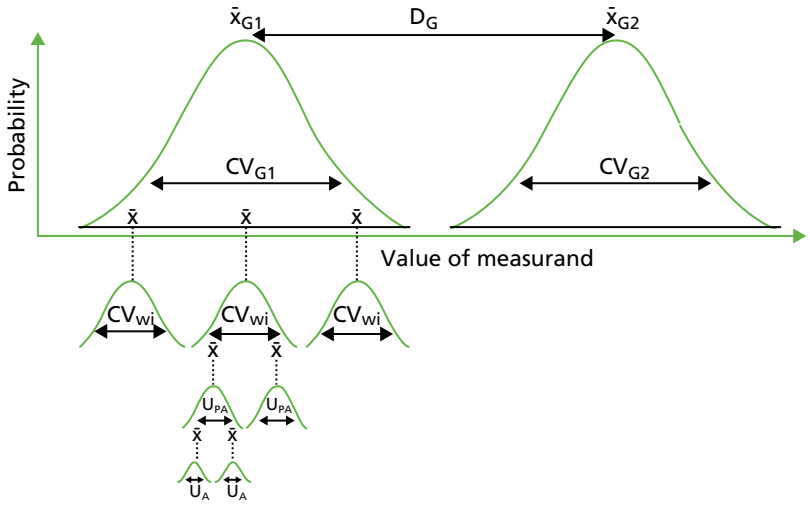

FIGURE 26 Gaussian bell curves illustrating the interdependency of analytical uncertainty (U_A), pre-analytical uncertainty (U_{PA}), within-individual biological variation (CV_{wi}) and within-group variation (CV_{G1} and CV_{G2}). As previously illustrated by Rorass *et al.*[270]

Measurement factors can impact negatively on clinical studies and trials as follows:

- *Risk of bias*. Subtle differences in measurement procedures between study arms can introduce systematic errors between groups of patients, which may be mistakenly interpreted as clinically relevant differences.[273] For example, a 2002 *Lancet* publication described a mass spectrometry-based proteomic signature for diagnosing ovarian cancer, with almost 100% sensitivity and specificity.[274] However, after the results proved difficult to reproduce, an independent analysis concluded that 'procedural differences' between the groups was the most likely explanation for the results.[275] Later studies have confirmed that mass spectrometry-based proteomic signatures are profoundly affected by pre-analytical sample-handling conditions, potentially leading to significant experimental bias.[276]
- *Concerns regarding reproducibility*. Differences in measurement procedures can introduce excessive variability between studies. This is a particular issue for systematic reviews and meta-analysis, in which reviewers do not generally take into account the robustness of measurement procedures or differences between studies. For example, evidence on the clinical validity and utility of the biomarker vascular endothelial growth factor (VEGF) has been complicated by differences in pre-analytical procedures between studies.[277,278]
- *Concerns regarding the applicability of research findings to clinical practice*. Often for reasons of pragmatism or cost, measurement procedures performed within a clinical study may differ substantially from those employed in clinical care. For example, it is not uncommon for trial samples to be frozen and analysed within a single batch. Although this reduces the study variance and makes a significant finding more likely, the results may not translate to clinical practice, where variability is usually higher as samples are measured over many days and using different batches of reagents. The effect of freeze–thawing may also introduce a systematic increase or decrease in biomarker concentration, invalidating clinical cut-off points and leading to a higher FP/FN rate in the clinic.

Although the updated STARD 2015[251] and QUADAS-2[30] documents both address important methodological issues concerning studies of diagnostic accuracy, neither of them address the issues associated with measurement. Furthermore, although several reporting guidelines have been produced in specific areas of the field,[279–281] we are not aware of any methods in use for evaluating the quality of measurement procedures within clinical studies. We suggest that this is limiting the ability of systematic reviewers and health technology assessors to fully evaluate risk and to model uncertainty within assessments. This has been highlighted in several recent NICE diagnostic assessment reports.[282–284]

Development of a framework for the Quality Assessment of Measurement Procedures

A framework for the Quality Assessment of Measurement Procedures (QAMPs) was developed within this study. An initial framework was constructed through consultation with experts and this was subsequently tested and refined. The final framework was then validated and its utility explored by applying it to the literature included in the meta-analysis for Nephrocheck (see *Chapter 3*).

Three medical laboratory professionals (Rebecca Kift, Leeds Teaching Hospitals NHS Trust; Ashley Garner, Leeds Teaching Hospitals NHS Trust; Catherine Sturgeon, NHS Lothian) were consulted concerning the scope and parameters for inclusion. The group agreed that the scope should be limited to 'in vitro diagnostic medical devices' as the requirements for non-IVDs (e.g. imaging devices or devices for taking physical or clinical measurements) may differ. The defining features of 'quality' with respect to measurement procedures were agreed as 'bias', 'reproducibility' and 'applicability'. It was agreed that parameters associated with biological within-individual variation, biological pre-analytical factors (also known as pre-pre-analytical factors), technical pre-analytical variation factors (also known simply as pre-analytical factors) and analytical factors would be included within the quality assessment framework. Existing standards and reviews in these areas were collated and reviewed to identify best practice in the field of IVD metrology. Once parameters had been identified, data extraction fields were created to capture the information required by a reviewer to quality assess each parameter within a research publication. The standards and guidelines identified and used are shown in *Table 38*.

TABLE 38 Standards and guidance documents used to develop the QAMPs framework

Organisation	Standard or guidance document	Type of uncertainty
ISO	BS EN ISO 15189:2012 Medical laboratories. Requirements for quality and competence[285]	Pre-analytical and analytical
IFCC	Quality indicators in laboratory medicine: a fundamental tool for quality and patient safety[286]	Pre-analytical and analytical
NIHR	RIPOSTE[287]	Pre-analytical and analytical
EQUATOR	Biospecimen Reporting for Improved Study Quality (BRISQ)[280]	Pre-analytical
EFLM	Standardization of collection requirements for fasting samples[288]	Pre-analytical
EFLM	Preanalytical quality improvement. In pursuit of harmony[289]	Pre-analytical
CLSI	H3-A6 Procedures for the Collection of diagnostic blood specimens by venepuncture[290]	Pre-analytical
CLSI	H18-A4 Procedures for the handling and processing of blood samples[291]	Pre-analytical
CLSI	GP16-A3 Urinalysis[292]	Pre-analytical
ISBER	Pre-Analytical variables affecting the integrity of human biospecimens in biobanking[293]	Pre-analytical
EQUATOR	STROBE-ME[281]	Biological, pre-analytical and analytical
NACB	Tumor Marker Quality Requirements Guidelines[294]	Biological, pre-analytical and analytical
EFLM	A checklist for critical appraisal of studies of biological variation[279]	Biological
ISO	17511:2003 In vitro diagnostic medical devices[295]	Analytical
ISO	13612:2002 Performance evaluation of in vitro diagnostic medical devices[296]	Analytical

continued

TABLE 38 Standards and guidance documents used to develop the QAMPs framework (*continued*)

Organisation	Standard or guidance document	Type of uncertainty
ISO	BS ISO 5725:1994 Accuracy (trueness and precision) of measurement methods and results[297]	Analytical
ACB	Measurement verification in the clinical laboratory[298]	Analytical
CLSI	EP32-R Metrological Traceability and Its Implementation[19]	Analytical
CLSI	EP26-A User Evaluation of Between-Reagent Lot Variation[20]	Analytical
CLSI	EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents[21]	Analytical
CLSI	EP21-A Estimation of Total Analytical Error for Clinical Laboratory Methods[22]	Analytical
CLSI	EP15-A3 User Verification of Precision and Estimation of Bias[23]	Analytical
CLSI	EP09-A3 Measurement Procedure Comparison and Bias Estimation Using Patient Samples[24]	Analytical
CLSI	EP07-A2 Interference Testing in Clinical Chemistry[25]	Analytical
CLSI	EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures[26]	Analytical
CLSI	I/LA30-A Immunoassay Interference by Endogenous Antibodies[27]	Analytical
CLSI	EP14-A2 Evaluation of Matrix Effects[28]	Analytical
FDA	Bioanalytical Method Validation[18,299]	Analytical
LGC	Evaluating measurement uncertainty in clinical chemistry[300]	Analytical
CLSI	Expression of Measurement Uncertainty in Laboratory Medicine[29]	Analytical
AAPS	Fit-for-Purpose Method Development and Validation for Successful Biomarker Measurement[301]	Analytical
AAPS	Recommendations for the Bioanalytical Method Validation of Ligand-binding Assays[302]	Analytical

AAPS, American Association of Pharmaceutical Scientists; ACB, Association of Clinical Biochemistry; EFLM, European Federation of Laboratory Medicine; EQUATOR, Enhancing the QUAlity and Transparency Of health Research Network; IFCC, International Federation of Clinical Chemistry; ISBER, International Society for Biological and Environmental Repositories; ISO, International Standards Organisation; LGC, Laboratory of the Government Chemist; NACB, National Academy of Clinical Biochemistry.

The initial framework for assessing the quality of measurement procedures was developed and further refined through an iterative process of testing, consultation and updating. Additional fields were included by the group if they were thought to be beneficial to the process. The nomenclature 'low risk', 'high risk' and 'unclear' was adopted for rating quality criteria, as used by The Cochrane Collaboration[303] and in the QUADAS-2 tool.[30] The QAMPs data extraction and quality assessment framework is shown in *Table 39*.

To initially validate the QAMPs template and demonstrate its utility, two reviewers extracted and quality appraised the literature included in the meta-analysis for Nephrocheck from *Chapter 2*.

Testing the Quality Assessment of Measurement Procedures framework using Nephrocheck as a case study

In total, four studies were included in the quality assessment, as identified from the searches reported in *Chapter 2*. Studies were first data extracted and then supporting evidence was collated while answering the signalling questions. Finally, a quality judgement was reached using the supporting evidence as the

TABLE 39 The QAMPs framework

Citation			
Authors:			
Title:			
Journal:	Year:	Pages:	
	Vol.:		
Description of the measurement procedure			
Features		**Index**	**Reference**
Name of analyte			
Test name			
Test platform/method used			
Manufacturer			
Sample matrix used [e.g. urine, serum, plasma (including type)]			
Pre-analytical biological			
Patient state (e.g. fed/fasted, sitting/standing, rested)			
Patient preparation			
Anatomical site and/or mechanism			
Time of sampling (e.g. before 0900, within 1 hour of reference test)			
Pre-analytical technical			
Sample collection (mechanism and use of stabilisation)			
Preprocessing handling, temperature, transport and time			
Sample processing (e.g. preservation, centrifugation conditions, timings and temperature)			
Storage (e.g. volume, temperature, duration, freeze–thaw cycles)			
Postprocessing handling and transport			
Consideration of differences between groups			
Standard operating procedures or quality assurance			
Other			
Analytical factors			
Sample blinding procedure			
Sample randomisation procedure			
Batching procedure			
Reference control materials			
Quality assurance procedures			
Patient inclusion/exclusion criteria			
Test failure rate and reasons for test failure			
Technical replication			
Performance evaluation			
Performance goals for:			
Precision			
Bias			
(method of calculation)			

continued

TABLE 39 The QAMPs framework (*continued*)

Performance evaluation
Within-individual biological variation
Pre-analytical factors
Total measurement uncertainty
Analytical validation
Full validation or verification
Analytical sensitivity:
Method (brief description)
Limit of blank (LOB)
Limit of detection (LOD)
Limit of quantitation (LOQ)
Analytical selectivity:
Method (brief description)
Cross-reactivity
Interference
Carry-over
Trueness:
Method (brief description)
Bias
Precision:
Method (brief description including M-Factors: time, calibration, operator and equipment)
Repeatability (range), CV%
Intermediate Imprecision (range), CV%
Reproducibility (range), CV%
Linearity and working range:
Method (brief description)
Other (e.g. lot to lot, antibody validation profile)
Signalling questions
Were measurement procedures different between groups?
Were measurement procedures described in enough detail to be repeated?
Were measurement factors appropriately controlled for?
Were measurement procedures applicable to the final clinical setting?
Risk of bias (high, low, unclear)
Risk of irreproducibility (high, low, unclear)
Risk of inapplicability (high, low, unclear)

CV%, coefficient of variation.

basis for transparency and discussion. When evidence was identified, risk was judged as being either high or low; only when there was insufficient evidence was risk judged as being uncertain. The results of the signalling questions are presented in *Box 1* and the quality assessment is summarised in *Table 40*. Full results from the data extraction are presented in *Appendix 7*.

Discussion

Quality assessment is now recognised as an essential component of systematic review and health technology assessment because of the marked heterogeneity between studies. Initiatives such as QUADAS[305] and QUADAS-2[30] have been routinely adopted into these processes and have proven useful in identifying studies that are at high risk of bias or inapplicability. Similarly, the introduction of reporting guidelines such as STARD[243] and STARD 2015[251] have improved reporting in the areas covered, assisting reviewers to assess quality and differences between studies, while helping researchers to accurately report

BOX 1 Results of the signalling questions

Meersch *et al.*[54]

Were measurement procedures different between groups?

- Uncertain. Pre-analytical and analytical study procedures were not reported in enough detail to be confident that bias had been avoided, for example no details were reported concerning sample blinding, randomisation and batching.
- In some patients, baseline creatinine level was used rather than creatinine level at time of enrolment; it is not clear if this was systematically different between patient groups.

Were measurement procedures described in enough detail to be repeated?

- Limited details were provided concerning the Nephrocheck test; not enough details were provided to repeat the study.
- Almost all parameters required to repeat the serum creatinine reference test were not described, even the name and manufacturer of the assay.

Were measurement factors appropriately controlled for?

- No. Albumin, bilirubin and methylene blue are known Nephrocheck interferents, which were not controlled for in the urine samples.
- Quality control procedures were not reported for the Nephrocheck test or for the creatinine reference test.
- The method and traceability of the reference test were not described.
- Performance characteristics of the reference test and index test were not described.
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was reported.
- No performance goals were reported.

Were measurement procedures applicable to the final clinical setting?

- Unclear as the study procedures not described in enough detail.
- Samples were frozen and thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing.

BOX 1 Results of the signalling questions (*continued*)

Bihorac *et al.*[33]

Were measurement procedures different between groups?

- No, but it is not clear whether samples were measured randomly and/or in batches, which may have introduced a systematic bias.

Were measurement procedures described in enough detail to be repeated?

- The urinary Nephrocheck test was generally reported in enough detail to be repeated.
- Several parameters required to repeat the serum creatinine reference test were not described.

Were measurement factors appropriately controlled for?

- No, the manufacturer's kit insert identifies albumin and bilirubin as interferents and recommends 'caution in interpreting Nephrocheck® results in patients with significant proteinuria or severe hyperbilirubinuria'.[304] Albumin (proteinuria and haematuria) and bilirubin (to a lesser extent) are associated with AKI. No attempt was made to identify and exclude these samples.
- Quality control procedures were not reported for the creatinine reference test.
- No validation or verification of the measurement systems was reported.
- No performance goals were reported.

Were measurement procedures applicable to the final clinical setting?

- No, measurements were conducted at three sites and the median of three measurements was used to determine diagnostic accuracy. Only a single measurement at a single site would be used in clinical practice, which may lead to less precise measurements.
- Samples were freeze–thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing.

Meersch *et al.*[55]

Were measurement procedures different between groups?

- Uncertain. Pre-analytical and analytical study procedures were not reported in enough detail to be confident that systematic bias between groups had been avoided, for example no details were reported concerning sample randomisation and batching, although laboratory investigators were blinded to clinical outcomes.
- Index and reference test samples were collected at different times; it was unclear whether this might introduce bias.

Were measurement procedures described in enough detail to be repeated?

- No, very limited data were provided concerning Nephrocheck and only the analyte name, matrix and time points were provided for creatinine.

Were measurement factors appropriately controlled for?

- No. Albumin, bilirubin and methylene blue are known Nephrocheck interferents, which were not controlled for in the urine samples.

BOX 1 Results of the signalling questions (*continued*)

- Quality control procedures were not reported for either the index or the reference test.
- The method and traceability of the reference test were not described.
- Performance characteristics of the index test and reference test were not described.
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was performed.
- No performance goals were reported.

Were measurement procedures applicable to the final clinical setting?

- No. Test was performed in patients aged < 18 years, which contradicts the instructions for use.
- Samples were frozen and thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing.

Hoste *et al.*[44]

Were measurement procedures different between groups?

- Pre-analytical procedures were described in adequate detail and did not appear to differ between patient groups.
- Although laboratory investigators were blinded to clinical outcomes, it is unclear whether samples were batched or randomised for analysis.
- Index and reference test samples were collected at different times; it was unclear whether this might introduce bias.

Were measurement procedures described in enough detail to be repeated?

- The urinary Nephrocheck test was reported in enough detail to be repeated, although it is not clear whether the measurements were performed in a single batch and randomised.
- In addition, it is not clear how long samples were frozen for.
- Several parameters required to repeat the serum creatinine reference test were not described.

Were measurement factors appropriately controlled for?

- No; albumin, bilirubin and methylene blue are known Nephrocheck interferents, which were not controlled for in the urine samples. The manufacturer's kit insert recommends 'caution in interpreting Nephrocheck® results in patients with significant proteinuria or severe hyperbilirubinuria'.[304]
- Quality control procedures were not reported for the creatinine reference test. The method and traceability of the reference test were not described.
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was performed.
- It is also not clear whether the samples were processed within 1 hour of collection.
- Performance characteristics and goals of the reference test and index test were not described.

Were measurement procedures applicable to the final clinical setting?

- Unclear; samples were freeze–thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing.

TABLE 40 Summary of the QAMPs results for Nephrocheck studies

First author and year	Risk of bias	Risk of irreproducibility	Risk of inapplicability
Bihorac 2014[33]	Unclear	High	High
Meersch 2014[55]	Unclear	High	High
Hoste 2014[44]	Unclear	High	Unclear
Meersch 2014[54]	Unclear	High	High

their findings.[306] However, factors associated with measurement have so far been excluded from such quality assessments, even though they are known to be a major source of bias, irreproducibility and inapplicability in clinical practice and increasingly in research studies. This could compromise patients' health if inappropriate test adoption decisions are made based on biased or inaccurate results. As far as we are aware, this is the first such initiative to assess the quality of measurement procedures used in clinical studies or trials.

Application of this framework within the four Nephrocheck case studies identified several measurement parameters that present a high risk of irreproducibility, including a failure to exclude samples with known interferents, a lack of internal and external quality control and a complete lack of analytical measurement verification in all studies. It also highlighted several issues that might affect the clinical applicability of test results, including freeze–thawing of samples in the absence of validation data and against the recommendations of the manufacturer, potentially biasing clinical cut-off points and overestimating precision; use of a device in an unvalidated patient population (i.e. aged < 18 years); and reporting the median value of three measurements from different laboratories. Furthermore, it identified several issues that made assessment of the risk of bias uncertain.

A key finding of this assessment was that the reporting of critical measurement parameters was very poor in the majority of studies and this severely hindered the reviewers' ability to assess their quality. Interestingly, all of the studies claimed to comply with the STARD reporting guidelines. In the absence of better reporting this framework will have limited utility, so this is an area that needs addressing. Unfortunately, the reporting guidelines already in existence [Biospecimen Reporting for Improved Study Quality (BRISQ)[307] and (STPROBE-ME)[308]] have not been widely adopted or promoted by journals. It is important to note that the issues pertaining to poor measurement procedures and the application of the QAMPs framework apply not only to diagnostic, prognostic or predictive accuracy studies of IVDs but also to any clinical trial or study using IVDs as end points or inclusion criteria. This includes Clinical Trials of an Investigational Medicinal Product (CTIMPs), especially in the era of precision medicine, with an increasing number of CTIMPs basing their eligibility criteria and end points on molecular biomarkers measured using IVDs.

Because of the complexity and scale of the subject matter, it might be tempting to create a long and highly detailed data extraction template and include more signalling questions. However, in the interests of pragmatism and user friendliness we attempted to keep the number of fields and signalling questions to a minimum. We believe that this will probably change over time as experience of using the framework develops and our understanding of the requirements and knowledge of reviewers and the critical 'at risk' parameters develops. For example, following the review of the results we identified that it might prove useful in future to include a specific field for 'sample exclusion' procedures.

Although the work presented here demonstrates the value of such an approach to quality assessment, the authors accept that this is only the first step towards developing such a framework and that further work is required. Potential areas for future research include refining the parameters and signalling questions,

validating the utility more widely and developing guidance for users. We have identified the following limitations that we hope to address in future work:

- *The framework has had limited input from the wider IVD community*. To address this we plan to set up a workshop with key external stakeholders and apply a more systematic approach to development of the framework.
- *Interpretation is limited by prior knowledge of the measurement factors affecting an IVD*. The instructions for use of IVDs must, by law, contain certain information on the analytical procedures and performance of a test. A formal data extraction process for instructions for use may provide a useful and pragmatic starting point against which to benchmark studies. However, additional parameters are often identifiable from the literature, perhaps requiring systematic review methods to be developed.
- *Limited evidence of utility*. Further validation of the approach is required across diagnostic, prognostic, predictive and monitoring contexts in addition to investigating its application in RCTs of CTIMPs.
- *The framework is currently limited to quantitative measurements*. There is a need to consider how to apply the framework to semiquantitative or qualitative measurements, for example next-generation sequencing.
- *Limited to IVDs*. There are similar issues with all diagnostics including imaging, physical measurements and clinical support algorithms.

Chapter 5 Economic evaluation

Introduction

There is currently growing interest in the use of decision modelling earlier in the research and development process for new health-care technologies.[309–311] This is, in part, a response to the high costs and failure rates of pre-regulatory Phase III trials, which is a key issue for tests, in particular, because of the difficult and often financially prohibitive task of linking test outcomes with subsequent treatment pathways. A decision model can be used in the early phases of the research pathway to synthesise current evidence on the effectiveness and cost-effectiveness of emerging technologies. For tests, models are a key resource to enable linkage of diagnostic accuracy evidence with downstream health and cost impacts. Furthermore, models can be used to identify key uncertainties in the evidence base that pose the most risk for clinical, regulatory and reimbursement decision-makers; this information can then be used to tailor the ongoing trajectory and design of research to target and reduce critical uncertainties and to avoid unnecessary and expensive large-scale trials when possible. This approach thereby enables both optimisation of future research resources and maximisation of research outputs.

The objective of the economic evaluation in the AKI-Diagnostics study was to (1) assess the potential cost-effectiveness of AKI biomarkers in an acute care setting, based on an evaluation of the current evidence base, and (2) determine the value of conducting further research into such biomarkers. The focus of this chapter is on the development of a decision model to determine the expected cost-effectiveness of AKI biomarkers; the implications for future research are explored further in *Chapter 6*.

Overview of the economic evaluation

A de novo decision-analytic model was constructed to evaluate the potential impact of AKI biomarkers within a hospital critical care setting. The model structure was developed using the findings from a model literature review, a focus group and expert consultation; model parameters were subsequently derived using data from the literature, analysis of individual patient clinical trial data and expert opinion. The model adopts a UK NHS and Personal Social Services (PSS) perspective, with all costs reported in 2015 prices and patient health measured in terms of QALYs. Future cost and health outcomes were discounted at an annual rate of 3.5%, as per current NICE guidance.[312]

Each of the tests included in the meta-analysis in *Chapter 3* (Nephrocheck, NGAL and cystatin C) was compared both individually against standard care monitoring and in a multiway incremental analysis. Cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER) and incremental net (health) benefit (INB) values and a range of sensitivity analyses was conducted to explore the impact of key model assumptions and parameter uncertainty on the results. The model was developed in line with current best practice standards[312–314] and was built and analysed using R software version 3.0.3.

Methods

Population and perspective

The base-case primary evaluation focused on the assessment of AKI biomarkers for a population of adult all-comers (aged $\geq$ 18 years) admitted to the hospital critical care unit. A secondary analysis was also conducted to assess outcomes in a subgroup of patients admitted to critical care post cardiac surgery.

These patients are known to be at particular risk of post-surgery renal failure and form a relatively homogeneous group who are managed in a controlled environment; they therefore represent a subgroup for whom there is a strong potential for management adjustments to lead to measurable changes in outcomes.

All analyses were conducted from a NHS and PSS perspective, as per the NICE reference case.[312] This aims to incorporate costs relating to NHS primary care, secondary care, community care and social care.

Testing strategies

Tests evaluated in the meta-analysis in *Chapter 3* (Nephrocheck, cystatin C and NGAL) were included in the economic evaluation. Cystatin C and NGAL are currently available across three alternative media (plasma, urine and serum); each of these was considered separately in the analysis, which, together with the Nephrocheck test, resulted in a total of seven testing strategies.

All tests were assumed to be used once on entry to the critical care unit in addition to standard care, consisting of daily serum creatinine and urine output testing. Although these new tests could also be used sequentially or in a monitoring context, the majority of evidence on the diagnostic accuracy of these tests relates to single-time usage and this was the focus of the current systematic review. Assessment of sequential and monitoring testing strategies was therefore deemed beyond the scope of this analysis but remains a key area for future research.

Costs and health outcomes

All costs are reported in 2015 prices (Great British pounds) and were inflated when necessary using an online converter.[315]

Health outcomes were measured in terms of QALYs. QALYs provide a generic measure of patient overall health and are a composite measure of patient survival weighted by quality of life (utility) over time, for example 1 year in full health is equivalent to 1 QALY, whereas 1 year at half-full health is equivalent to 0.5 QALYs. Expression of health benefit in terms of QALYs allows decision-makers to make a direct comparison between the cost-effectiveness of interventions across different disease areas and indications; NICE[312] currently recommends the use of QALYs in cost-effectiveness analyses.

Literature review of acute kidney injury economic models

A literature search was conducted in February 2015 and updated in March 2016 to identify economic models of AKI to help inform the model structure and parameters.

The following databases were searched: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Central register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and NHS EED (NHS Economic Evaluation Database). Search strategies included concepts for AKI and economic models (see *Appendix 8* for the full database details and an example search strategy). All search results were screened by one health economist using a two-stage process: initial abstract screening to identify potentially relevant references followed by full-text screening to determine final inclusion.

The initial inclusion criteria aimed to identify any models including AKI health states, regardless of setting. For the updated search only economic models assessing AKI biomarker testing strategies were included, as these were deemed to be of most use to the project at that stage.

The original search identified 235 references (179 after removal of duplicates), which increased to 296 (48 after removal of duplicates) references in the update search. In total, 11 studies were included in the review,[187,205,316–324] two of which were economic evaluations of AKI biomarkers[187,205] (*Figure 27*).

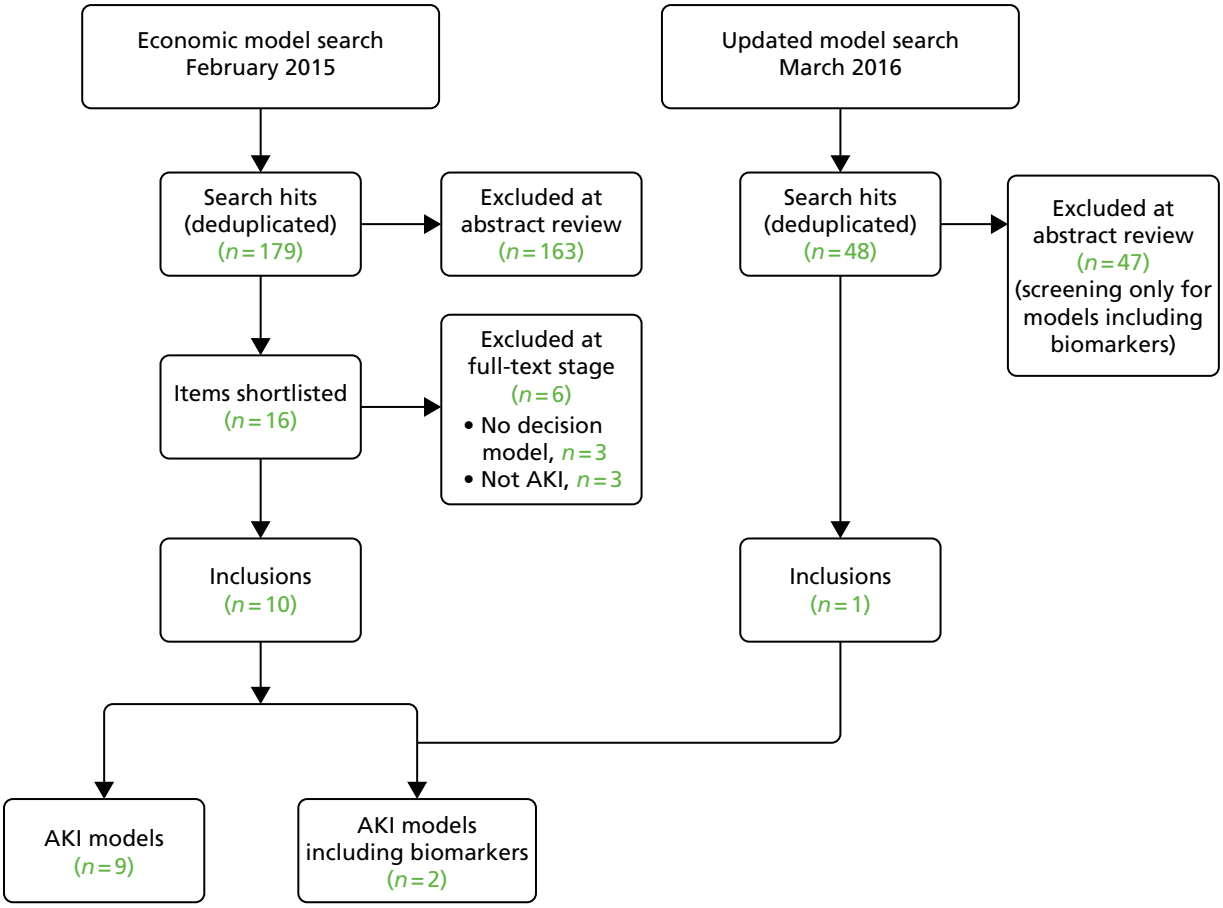

FIGURE 27 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the AKI economic decision model search.

Details of the included models are presented in *Table 41*. The majority of studies not looking at biomarkers were concerned with assessing different dialysis modalities or contrast media to prevent or treat renal injury. These studies incorporated a range of health states, including within-hospital states such as dialysis/no dialysis, AKI/no AKI, AKI severity levels and hospital death, and post-discharge states, such as alive with/without dialysis, CKD, end-stage renal disease (ESRD), transplant and death.

Two studies assessed the cost-effectiveness of biomarkers for the early diagnosis of AKI in a critical care setting and are of greatest relevance to this study.

Shaw *et al.*[205]

This study assessed the lifetime cost-effectiveness of urinary NGAL for the early diagnosis of AKI after cardiac surgery compared with standard care testing of blood urea nitrogen, blood creatinine and urine output. The base case considered a 67-year-old man after coronary artery bypass graft surgery. The authors stated that they adopted a UK societal perspective; however, it was subsequently acknowledged that they could not include indirect costs because of difficulties in estimating them and the final analysis appears to have been restricted to a NHS perspective, with costs reported in 2008 Great British pounds.

The authors presented a simplified decision tree diagram of their model, in which patients in the testing arm were monitored using NGAL on four occasions (2 hours after surgery and then every 6 hours), with a single elevated result leading to early treatment for AKI. AKI severity was defined in terms of the RIFLE criteria, with each severity level being associated with a specific mortality risk, critical care length of stay and long-term CKD risk. The authors assumed a non-specific treatment modality for AKI including various dialysis modalities, avoidance of nephrotoxic agents, fluid management and an additional nephrologist

TABLE 41 Acute kidney injury economic decision model review: included studies

First author and year	Country	Intervention(s)	AKI status	Perspective	Time horizon	Model type	Health states included	Main result
Chicaiza-Becerra 2012[316]	Colombia	Iso- and low-osmolality contrast media	Outpatients at high risk of renal injury	National Health System	Lifetime	Decision tree	Treatment + no AKI + death/no death; treatment + AKI + dialysis/no dialysis + death/no death	Lopamidol and Iodixanol dominated all other alternatives. Lodixanol vs. Iopamidol = US$14,660/life-year gained
De Smedt 2012[317]	Belgium	CRRT, IRRT and conservative (CONS) treatment	AKI in the ICU	Payer perspective	2 years	Area under the curve analysis	NA	CRRT was the most effective and costly strategy. CONS dominated IRRT. ICERs: CRRT vs. IRRT = €114,012 per QALY; CRRT vs. CONS = €590,410 per QALY
Desai 2008[318]	USA	Daily vs. alternate-day haemodialysis	60-year-old man in ICU with AKI	Societal	Lifetime	Markov model (annual cycle length)	Hospital death, post-discharge CKD ± haemodialysis, no CKD, transplant waiting list (± dialysis), transplant failure/success	ICER for daily vs alternate-day haemodialysis: US$5084 per QALY
Erstad 1999[319]	USA	Albumin–furosemide complex vs. sequential therapy	Acute oliguric renal insufficiency	Teaching hospital	Short (approximately 6 months)	Decision tree	Treatment + successful (no dialysis); treatment + unsuccessful (dialysis)	Cost per averted dialysis: albumin–furosemide complex = US$28,807; sequential therapy = US$109,350
Ethgen 2015[320]	USA	CRRT vs. IRRT	AKI in the ICU	Third-party public payer	Lifetime	Markov model (daily cycle first 5 years; yearly thereafter)	CRRT in ICU, IRRT in ICU, post discharge ± dialysis, death	CRRT dominated IRRT (based on ICER)
He 2010[321]	USA	Nesiritide Natrecor; Johnson & Johnson, New Brunswick, NJ, USA) vs. placebo for prevention of AKI	Post cardiac surgery	NA (no costs included)	NR	Decision tree	Hospital death ± dialysis, discharged alive ± dialysis	Absolute risk reductions for dialysis and hospital death for nesiritide vs. placebo = 1.3% and 3.3% respectively
Iannazzo 2014[322]	Italy	Iodixanol vs. low-osmolar contrast media	Patients with intravenous contrast media CT	Health-care provider	Lifetime	Markov model (1-month cycle)	AKI free, AKI, myocardial infarction, death	Incremental cost per life-year gained: iodixanol dominated low-osmolar contrast media

First author and year	Country	Intervention(s)	AKI status	Perspective	Time horizon	Model type	Health states included	Main result
Kerr 2014[323]	UK	NA (assessment of costs and QALYs)	72-year-old patients with AKI in hospital	English NHS	2 years post discharge	Markov model (annual cycle)	Normal kidney function, AKI, CKD, ESRD ± RRT, transplant for ESRD, death	Lifetime cost for all AKI inpatients post-discharge care = £179M; lifetime QALY loss = 1.4 per person
Klarenbach 2009[324]	Canada	Standard- or high-dose CRRT vs. IHD	≈60-year-old requiring RRT in ICU	Health-care provider	Lifetime	Mixed decision tree and Markov model	Tree (hospital): dead, treatment ± recovery. Markov model (discharged): alive ± dialysis, dead	CRRT resulted in equivalent QALYs but was C$3679 more costly than IHD
Shaw 2011[205]	UK	NGAL vs. standard care	67-year-old man undergoing CABG surgery	Societal	Lifetime	Decision tree	AKI/no AKI, NGAL elevated/normal, AKI failure/injury, CKD/no CKD, treatment/no treatment, CKD/no CKD post discharge, death	NGAL dominated standard care
Petrovic 2015[187]	USA	Cystatin C, urine NGAL and uL-FABP vs. standard care	Children with congenital heart disease post cardiac surgery	Health-care payer	Lifetime	Markov model	AKI/noAKI, AKI risk/injury/failure, discharged, death, long term no CKD, CKD, ESRD, transplantation, death	ICERs vs. standard care: US$5959 (uL-FABP), US$7077 (cystatin C), US$9315 (NGAL urine)

CABG, coronary artery bypass graft; CRRT, continuous renal replacement therapy; CT, computerised tomography; dominated, less costly and more effective than the next best alternative; IHD, intermittent haemodialysis; IRRT, intermittent renal replacement therapy; NA, not applicable; NR, not reported; uL-FABP, urine liver fatty acid-binding protein.

visit. NGAL sensitivity (0.379) and specificity (0.812) were derived from two diagnostic studies of 72 and 426 patients (smaller studies were not considered) and, in the absence of data, the accuracy of sequential tests was assumed to be equivalent. Instigation of early AKI treatment in the risk stage was assumed to result in a 25% reduction in progression to the injury or failure state.[72,140] The cost of each NGAL test was £25. Discounting of future costs and outcomes was not reported.

The expected lifetime costs and QALYs were £4244 and 11.86 for urine NGAL and £4672 and 11.79 for usual diagnosis. NGAL dominated usual care, being more effective and less costly, and had a 100% probability of being cost-effective at a willingness-to-pay threshold of £30,000. NGAL remained the preferred strategy even in a 'conservative scenario' in which the treatment effect was halved from 25% to 12.5%. The most influential inputs identified from sensitivity analyses were the previous probability of AKI and the probability of developing CKD.

This study was funded by a grant from Abbott Diagnostics (Lake Forest, IL, USA), the manufacturer of an assay kit for the measurement of NGAL in urine.

Petrovic *et al.*[187]

This study assessed the lifetime cost-effectiveness of cystatin C (serum), NGAL (urine) and urine liver fatty acid-binding protein (uL-FABP) for the diagnosis of AKI in children (aged < 18 years) after cardiac surgery compared with standard care of serum creatinine monitoring. The analysis adopted a US third-party payer perspective (price year not reported).

The model consisted of an initial decision tree in which patients were divided into no AKI and AKI RIFLE severity groups. Patients in the testing arms were assumed to be tested 2 hours after surgery and were subsequently separated into TP/FP and TN/FN groups according to the test accuracies. Patients could then either die in hospital (with mortality dependent on AKI stage) or survive to discharge and then die or survive post discharge. A Markov model was used to capture the long-term risks of CKD (stages 1–4), ESRD, renal transplant and mortality for patients experiencing AKI. All cost and health outcomes were discounted by 3% per annum.

Sensitivity (cystatin C = 0.54; NGAL = 0.63; uL-FABP = 1) and specificity (cystatin C = 0.54; NGAL = 0.63; uL-FABP = 1) values were derived from a single study including 112 paediatric subjects.[184] Therapy as a result of early AKI diagnosis was assumed to result in a 25% improved outcome for AKI patients. Test costs were US$18.94 for cystatin C, US$17.81 for NGAL and US$24.38 for uL-FABP. Probabilistic sensitivity analysis was conducted; however, no variance data were presented for the parameter distributions.

The testing strategies were all more effective and more costly than standard care, with expected lifetime costs of US$18,463 for cystatin C, US$15,304 for NGAL and US$14,126 for uL-FABP compared with US$5608 for standard care and QALYs of 5.15, 5.16, 5.21 and 3.78 respectively. Cystatin C and NGAL were both dominated by uL-FABP, which produced an ICER of US$5959 per QALY compared with standard care and had a 100% probability of being cost-effective at a willingness-to-pay threshold of US$50,000 per QALY. The authors declared no conflicts of interest for this study.

Focus group

A focus group was held on 26 February 2015 with two clinicians (nephrologists) and two patient representatives with experience of chronic kidney failure. The primary aim was to understand the care pathway for patients diagnosed with AKI in a critical care setting, with secondary aims of understanding the impact of AKI and its treatments on patient outcomes and quality of life. The session was co-ordinated by two qualitative research officers (NW and KVC) and two health economists (DM and AS). The group discussion followed a topic guide, which was focused on developing a diagrammatic representation of the patient pathway for someone experiencing AKI in critical care. Interviews were audio recorded and transcribed verbatim by a third party and framework analysis was undertaken to systematically sift, chart and sort material by key themes.

The findings were outlined according to four subsections, briefly outlined below:

1. *People at risk of developing AKI*. There are many triggers for AKI and there are multiple groups at risk, including patients with long-term conditions (CKD/heart failure), patients with comorbidities and the elderly. In the hospital patients on any ward may develop AKI and may have previously had normal renal function.
2. *Diagnosing AKI*. Multiple tests and assessments can be used to diagnose AKI in hospital. Some hospitals now use electronic alert systems but there is currently a lack of standardised practice in this area.
3. *Treating AKI*. After diagnosis, treatment generally consists of a non-specific care bundle including fluid assessment, medication review and additional investigations and monitoring. Treatment procedures may vary depending on the cause of the AKI, individual patient characteristics and hospital procedures.
4. *Long-term health consequences of AKI*. Post treatment some patients completely recover whereas others may go on to develop CKD and require dialysis or renal transplantation.

The themes identified in the focus group generally support NICE-identified pathways for AKI.[1,325–327] Particular issues identified that were pertinent to the development of the decision model included (1) the multiple aetiologies of AKI and the associated heterogeneity of the AKI population, (2) the non-specific nature of AKI treatment and (3) the need to capture downstream risks of CKD.

Model structure

The model structure was developed using the findings from the literature review and focus group, NICE guidelines[1,325–327] and expert feedback. A simplified representation of the model is presented in *Figures 28* and *29*.

The model is split into an initial decision tree (see *Figure 28*) and a subsequent modified Markov model (see *Figure 29*). The decision tree separates patients into cohorts depending on their AKI status and test results; patients then enter the main Markov model, which describes patients' health-care pathway over the duration of their hospital stay and post-discharge follow-up. In the Markov model patients occupy different health states and may move between those states over time, with movement triggered by events such as AKI onset, AKI progression, development of CKD and mortality. Each health state is associated with a specific cost and quality of life (utility) value such that over time patients accumulate costs and health benefits over model cycles of a defined length of time. The model is run separately for each of the specified cohorts within each of the arms (standard care and testing arms) to obtain an average cost and average QALYs (quality of life + survival), from which cost-effectiveness is calculated.

Initial decision tree model

The initial decision tree separates patients into cohorts depending on their AKI status and (for the intervention arms) their additional test results. In the standard care arm, patients are split into 'AKI' and 'no AKI' cohorts. Patients in the AKI cohort either arrive in the critical care unit (also hereafter referred to as the ICU) with pre-existing AKI or are destined to develop AKI at some point during their stay; patients in the no AKI cohort are those who maintain normal renal function throughout their critical care stay. Standard care testing is assumed to be perfect, such that all patients in the baseline model are correctly identified as either having or not having AKI.

Patients in the testing arms of the model are assumed to receive an additional test on admission to the critical care unit alongside standard care testing. It is expected that patients arriving in critical care with known moderate or severe AKI (KDIGO stages ≥ 2) would not receive additional testing; these patients follow the baseline AKI cohort pathway. All other patients are assumed to be tested and are separated into four cohorts according to the accuracy of the test results, that is, TPs, FNs, TNs and FPs.

Main Markov model

The Markov model consists of two periods: a hospital period, to assess patients' short-term outcomes, and a follow-up period, to assess patients' long-term outcomes post hospital discharge.

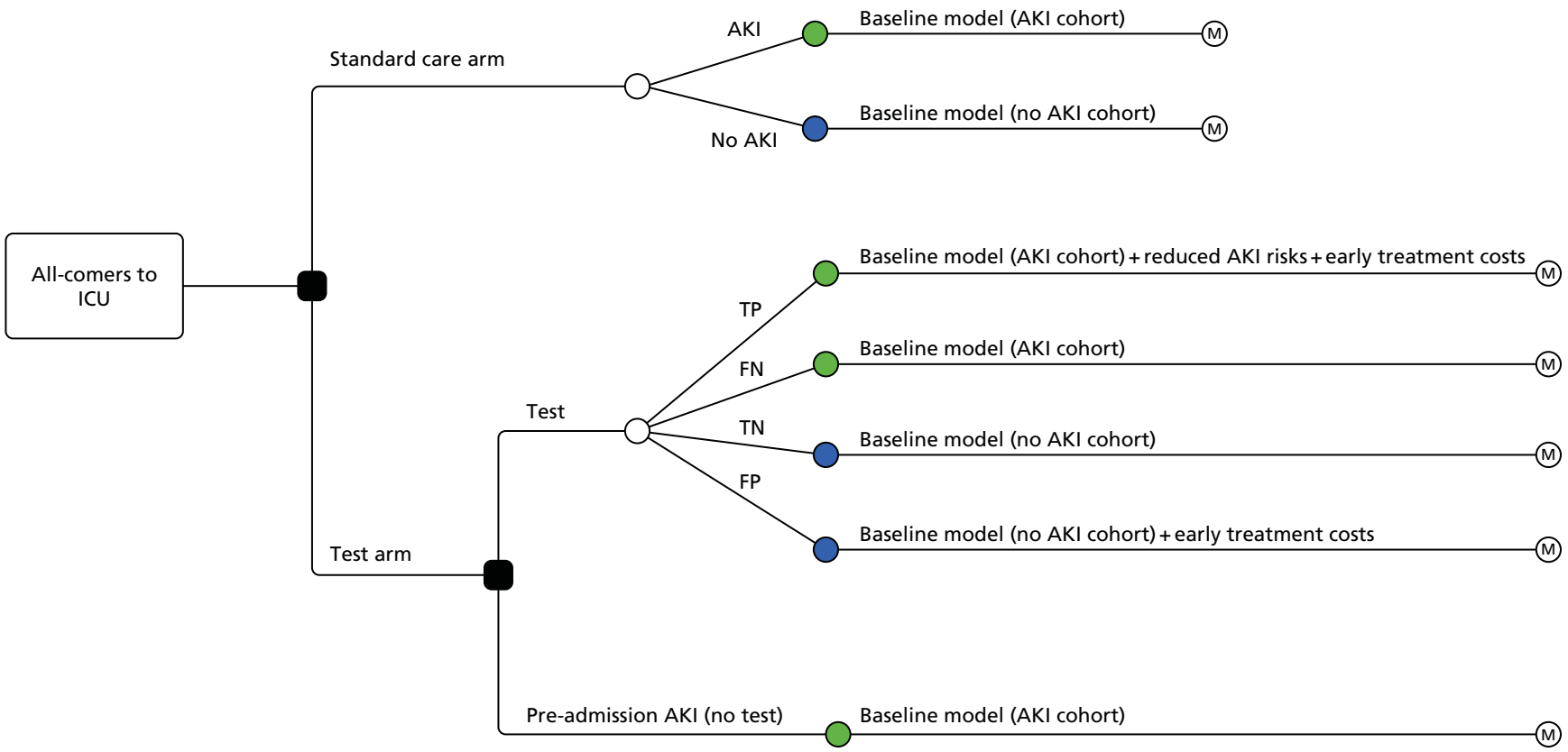

FIGURE 28 Model structure: initial decision tree. M, Markov model.

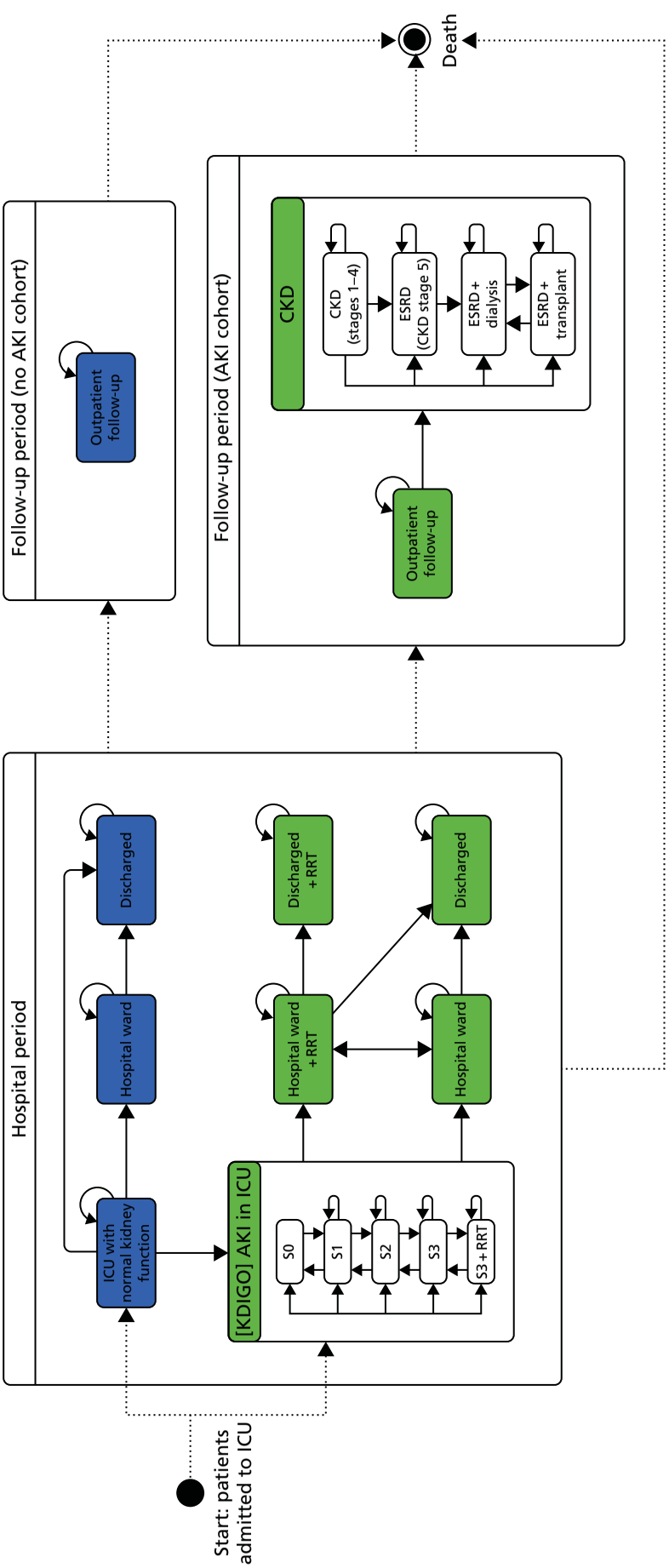

FIGURE 29 Model structure: main Markov model.

Hospital period (days 1–90)

The hospital period adopts daily cycles and runs from day 1 (entry to critical care unit) to day 90 to capture rapid changes in patients' health during their critical care stay.

The model is separated into no AKI and AKI cohort states. Patients with no AKI start in the 'ICU with normal kidney function' state and over time may remain in critical care, be discharged directly into the community or be transferred to a general ward before being discharged. Patients in the AKI cohort are classified into one of five health states according to the severity of their AKI on entry to the critical care unit: current normal kidney function (but destined to get AKI) (stage 0; S0) and the four KDIGO AKI classifications – stage 1 (S1), stage 2 (S2), stage 3 (S3) and stage 3 plus RRT (S3 + RRT). Patients may deteriorate or improve over time (moving to higher or lower severity states). From the ICU health states, patients may be transferred to a hospital ward (with or without RRT) or be discharged home (with or without RRT). Post-discharge patients are assumed to remain in their discharged state for the remainder of the hospital period. By definition, the onset of CKD requires a minimum of 3 months of persistent renal failure;[328] CKD is therefore not included within the hospital period, but is captured in the follow-up model.

Follow-up period

The follow-up period aimed to capture patients' long-term outcomes post hospital discharge. It was run from 90 days post critical care admission for the patients' lifetime (capped at 100 years) using annual cycles. A half-cycle correction was applied in the follow-up period of the Markov model to account for the continuous flow of patients between Markov states (i.e. in reality not all patients transition at the beginning/end of a year).

All patients in the no AKI cohort who are still alive at the end of the hospital period model are assumed to move to the 'outpatient follow-up' state in the follow-up model, where they remain, subject to an annual mortality risk.

Patients in the AKI cohort who are still alive and not on RRT at the end of the hospital period similarly move to a separate 'outpatient follow-up' state, where they experience elevated mortality and CKD risks compared with the no AKI cohort. Patients receiving RRT at the end of the hospital period (in the ICU, hospital ward or discharged plus RRT states) are assumed to have CKD and move to the 'CKD (stages 1–4)' state. From the CKD state, patients may go on to develop ESRD, with or without maintenance dialysis, or require a renal transplant. If the transplant is successful patients remain in the transplant state; if the transplant is unsuccessful patients are assumed to return to the 'ESRD + dialysis' state, but may go on to receive a subsequent transplant.

In all states for both cohorts, patients experience a mortality risk that is dependent on their current health state.

Impact of the tests

All patients in the testing arms without known pre-existing AKI (KDIGO stage ≥ 2) are assumed to be tested and, therefore, receive an additional cost of testing. Other baseline risks and costs in the model are adjusted according to the test result, as described in the following sections.

True positives

Patients with a TP test result are split into two subgroups. Patients with no or mild AKI (KDIGO stages ≤ 1) according to concurrent standard care test results are assumed to be able to benefit from early AKI intervention as a result of the positive test result. These patients follow the baseline AKI cohort but with an additional cost of early treatment and reduced risks of future AKI progressions [i.e. from (S0 or S1) to (S2, S3 or S3 +RRT)] and AKI-associated mortality (mortality in state S3 + RRT). Patients with moderate or severe AKI (KDIGO stages ≥ 2) according to concurrent standard care tests are assumed to not be able to benefit from early intervention. These patients follow the baseline AKI cohort model with no changes to risks or costs.

False positives
Patients with a FP result incur an unnecessary additional cost of early AKI intervention; however, in the base case this is assumed to have no detrimental impact on patients' health. These patients follow the baseline no AKI cohort with no risk changes applied.

True negatives
Patients with a TN result follow the baseline no AKI cohort with no additional changes applied to the baseline risks or costs.

False negatives
Patients with a FN result receive a concurrent or eventual AKI diagnosis through standard care daily testing. In the base case these patients are assumed to incur no harm from the inaccurate test result and follow the baseline AKI cohort.

A range of alternative assumptions regarding the impact of testing are explored in the sensitivity analysis reported later in this chapter.

Model parameter literature review

Primary searches
To help inform model parameter estimation, a literature review was conducted in July and August 2015 across the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and The Cochrane Library. Six search strategies were devised to identify evidence on (1) AKI costs, (2) AKI utilities, (3) AKI risks, (4) CKD costs, (5) CKD utilities and (6) CKD risks. Date limits and UK filters were used in some searches to target studies with recent, UK-based data (i.e. of most relevance to the model). Full details are reported in *Appendix 9*.

For AKI searches, studies were included if they reported on relevant outcomes for adult patients with or recovering from AKI, or on dialysis, and had a hospital critical care or post-critical care setting. For CKD searches, studies were included if they reported on relevant outcomes for adult patients with a primary condition of CKD, who were on chronic dialysis or who had undergone a renal transplant, across any setting. Relevant outcomes were defined as follows:

- cost searches: UK patient or health-care costs
- utility searches: direct utilities reported on multiattribute utility indexes or through direct valuation exercises [i.e. EuroQol-5 Dimensions (EQ-5D),[329] Short Form questionnaire-6 Dimensions (SF-6D)[330] or time trade-off (TTO)/standard gamble (SG) utilities]
- AKI risk searches: AKI incidence or progression, mortality, dialysis dependence, progression to CKD or ICU/hospital length of stay
- CKD risk searches: incidence of CKD, ESRD or transplants post AKI, progression or recovery rates for these conditions, dialysis dependence, transplant success and mortality.

All screening and data extraction was conducted by one health economist (AS). Citations were initially screened by title and abstract, followed by full-text screening to determine inclusion. In cases in which the reviewer was unsure about study inclusion a second reviewer (DM or PH) was consulted. All papers screened at the full-text stage were hand-searched for additional relevant references. Search results were stored in six EndNote version X12 libraries [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] and data extraction was conducted using a standard extraction form in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

Across the six searches, 1153 potentially relevant citations were identified after removal of duplicates (*Figure 30*). In total, 129 references were included in the review: four for AKI costs,[323,331–333] none for AKI utilities, 40 for AKI risks,[323,331–369] 33 for CKD costs,[323,370–401] eight for CKD utilities[402–409] and 44 for CKD risks.[370,373,410–451]

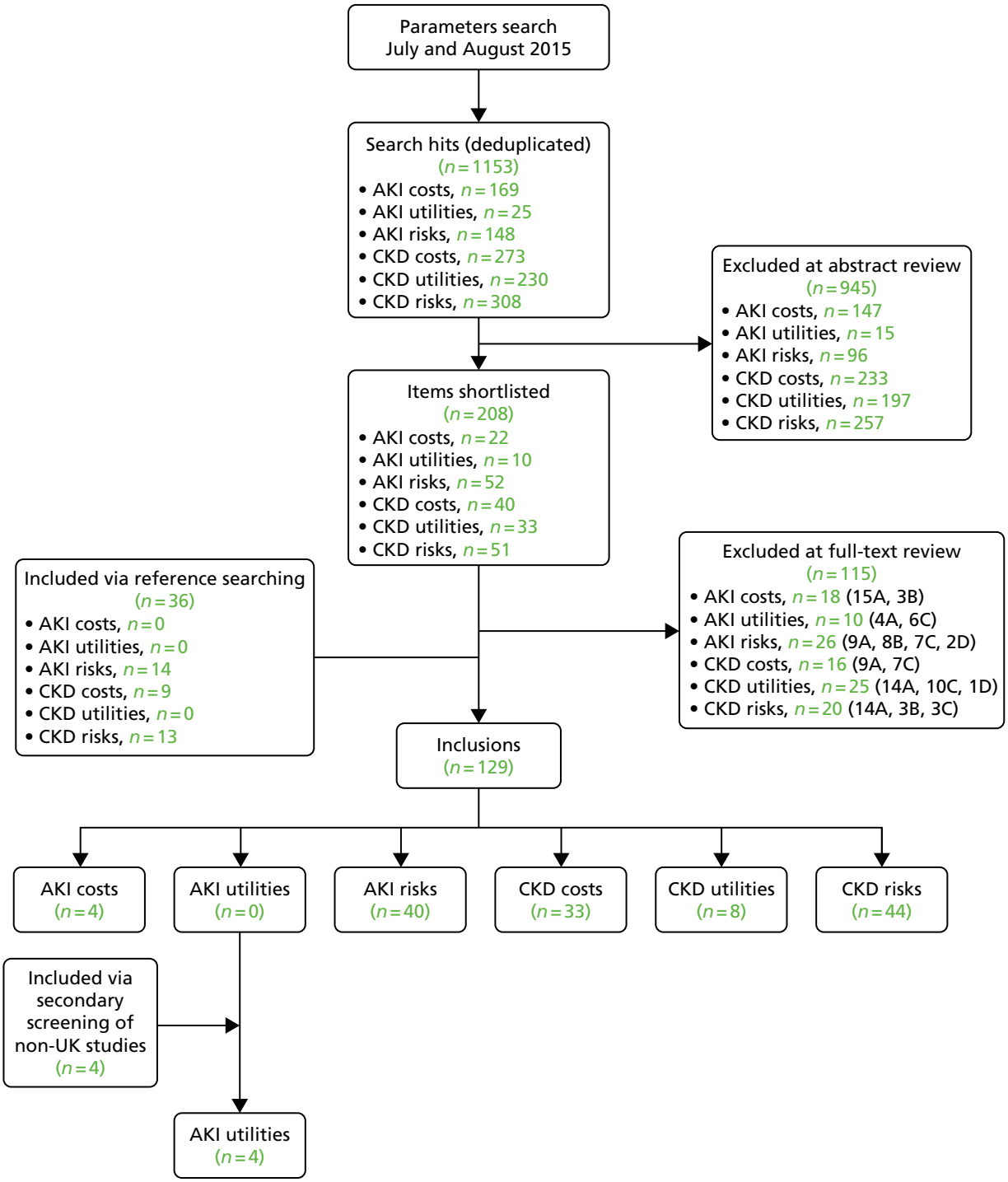

FIGURE 30 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the model parameter searches. Reasons for exclusion: A = no relevant outcome reported; B = non-UK study (when this was applied as an additional exclusion criteria); C = inappropriate study type (e.g. editorial); D = date (when date restrictions were applied).

For the AKI utilities search, no UK studies or international evidence syntheses were identified according to the original scope of the search. Secondary screening and citation tracking of the search results was therefore conducted to identify any relevant non-UK studies, with no date restrictions, leading to four non-UK-relevant papers being included.[317,452–454]

Tables 42–44 provide a summary of the included studies. The majority of evidence identified related to studies reporting outcomes for patients with CKD. Of these studies, the following were identified as being of particular use for model parameter estimation: (1) a comprehensive worldwide meta-analysis reporting CKD, dialysis and transplant health state utilities;[402] (2) a large ($n = 7246$) UK randomised multicentre clinical trial reporting CKD, dialysis and transplant costs, as well as the probabilities of transition between CKD, dialysis and death;[370] and (3) the UK Renal Registry annual report, which reports key data on annual transitions between ESRD, dialysis, transplant and mortality states[410] (note that model parameters were derived from the subsequently published 2015 version of this report).[455]

Limited evidence on costs and utilities for AKI was identified: no UK utility studies were identified (compared with nine in the CKD search) and only three UK cost studies were identified (compared with 33 for CKD), none of which reported disaggregated or per-patient critical care costs that could be used to inform the model health state costs. For AKI risks, a worldwide systematic review[334] was identified that reported an ICU KDIGO AKI incidence of 31.7% (95% CI 28.6 to 35.0) in an all-comer population and 24.3% (20.4 to 28.8) in a post-cardiac surgery population.[456] This was deemed to be the most reliable study to inform the estimates of AKI incidence. It was noted, however, that other clinical studies reported incidences both above and below the reported 95% CIs;[334–342] this parameter was therefore included in the sensitivity analysis.

Additional searches

Two additional searches were conducted in an attempt to identify data on (1) cost and quality of life outcomes for patients treated in the ICU (AKI and no AKI cohorts) and (2) the impact of early AKI intervention.

Costs and utilities

Subsequent searching of BioMed Central *Critical Care* journal publications identified a high-quality recent publication reporting follow-up costs and mortality for a large cohort of all-comer patients ($n = 5259$) treated in ICUs across Scotland (published after the date of the review).[457] No further searches were therefore conducted for ICU/follow-up costs.

To help inform ICU utility estimates, an additional search was undertaken using the Cost-effectiveness Analysis (CEA) Registry[458] and School of Health and Related Research Health Utilities Database (ScHARRHUD) databases,[459] which provide specific health state utility search functions. Key terms relating to hospital wards and the ICU were searched to identify UK papers reporting direct utilities on multiattribute utility indexes or through direct valuation exercises (i.e. SF-6D or TTO/SG utilities). Three relevant studies were identified[460–462] and are summarised in *Table 45*. The studies by Hernández *et al.*[460] and Cuthbertson *et al.*[461] measured EQ-5D outcomes for all-comer ICU populations and were deemed to be of most relevance for the model.

Impact of early acute kidney injury intervention

A key parameter in the model concerns the impact of early AKI intervention on patient health outcomes, that is, the 'treatment effect' parameter linked to tests resulting from early identification of AKI. Two previous economic evaluations of AKI biomarkers[187,205] identified in the model review assumed a uniform 25% reduction in subsequent AKI risks as a result of early diagnosis. However, in both studies no evidence base was cited to support this key parameter estimate.

A literature search was conducted in March 2015 to identify reviews of early treatment/preventative strategies for AKI in the ICU across the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE and The Cochrane Library. The search aimed to identify UK reviews including early treatment/preventative strategies for adults with AKI in the ICU, published in the last 5 years. Search strategies included the search concepts acute kidney injury, critical care, early treatment and treatment effectiveness (see *Appendix 10* for full details).

TABLE 42 Included studies from the AKI and CKD utility searches

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Utility measure	Reported utilities
AKI utilities[a]							
Johansen 2010[452]	USA	377	Mean 58	70.6	AKI in ICU as a result of necrosis plus sepsis or organ failure, requiring RRT	HUI	Mean utility at 60 days post randomisation: 0.40 (SD 0.37)
De Smedt 2012[317]	Belgium	203	Adults	NR	AKI in ICU requiring RRT with serum creatinine > 2 mg/dl	SF-36	Mean utility at 20.1 months post hospital admission: 0.69 (SE 0.15, 95% CI 0.67 to 0.71)
Åhlström 2005[453]	Finland	153	Mean 56	69	AKI in ICU or ward requiring RRT	EQ-5D	Median utility at median follow-up of 2.4 years: 0.68 (IQR 0.53–0.85) for ICU patients vs. 0.86 (IQR 0.83–0.88) in matched general population
Hamel 1997[454]	USA	57	Median 61	42	AKI in ICU or ward requiring RRT with an average expected 6-month survival of 50%	TTO	Mean utility at 6 months follow-up: 0.84 (SD 0.25)
CKD utilities (all UK studies or reviews)							
Neri 2012[403]	UK and USA	144 (UK patients)	Mean 52	61	Kidney transplant patients. Mean time since transplant 5.3 years	EQ-5D	Median: 0.73 (IQR 0.23). Mean utility: transplant with CKD stages 1–2: 0.64; CKD stage 3: 0.58; CKD stage 4: 0.49; CKD stage 5: 0.28. Mean disutility of CKD stage 5 vs. CKD stages 1–2: –0.38
Neri 2010[404]	UK and USA	209 (UK patients)	Mean 53	NR	Kidney transplant patients. Mean time since transplant 5.6 years	EQ-5D	(Kidney transplant patients) Mean utility: transplant with CKD stages 1–2: 0.74; CKD stage 3: 0.69; CKD stage 4: 0.61; CKD stage 5: 0.39
Wyld 2012[402]	USA = 99, Europe = 151, other = 76	Number of utility estimates: CKD pretreatment = 25, dialysis = 226, transplant = 66, conservative care = 3	NR	NR	CKD, dialysis and transplant	Utilities on 0–1 scale (review)	Pretreatment CKD stages 3–5: 0.79 (95% CI 0.70 to 0.89); conservative care: 0.62 (95% CI 0.43 to 0.82); CKD stages 3–5 dialysis: 0.70 (95% CI 0.62 to 0.78); utility decrement vs. transplant: –0.02, –0.2 and –0.11 respectively; transplant: 0.85

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Utility measure	Reported utilities
Wyld 2010[405]	NR (170 studies included)	> 56,000	NR	NR	CKD, dialysis and transplant	Utilities on 0–1 scale (review)	Pretreatment CKD: 0.56 (95% CI 0.52 to 0.60); conservative care: 0.66 (95% CI 0.30 to 1.00); CKD stages 3–5 dialysis: 0.52 (95% CI 0.50 to 0.53); home dialysis 0.57 (95% CI 0.53 to 0.61) vs. hospital 0.50 (95% CI 0.57–0.63); transplant: 0.60 (95% CI 0.57 to 0.63)
Blakeman 2014[406]	UK	436	Mean 72.1	42	CKD stage 3	EQ-5D	Mean baseline utility CKD stage 3: 0.67 (SD 0.3)
Liem 2008[407]	NR (27 studies included)	27 studies included	Mean range 42.1–60	Range 50–63	ESRD requiring dialysis or transplant patients	TTO, SG or EQ-5D (review)	(ESRD dialysis) TTO values: HD: 0.61 (95% CI 0.54 to 0.68); PD: 0.73 (95% CI 0.61 to 0.85). EQ-5D values: HD: 0.56 (95% CI 0.49 to 0.62); PD: 0.58 (95% CI 0.50 to 0.67). SG values: HD: 0.75 (95% CI 0.57 to 0.92). TTO transplant: 0.78 (95% CI 0.63 to 0.93). EQ-5D transplant: 0.81 (95% CI 0.72 to 0.90)
Lung 2011[408]	USA = 2, UK = 1, Japan = 1	Mean of included studies = 184.6	NR	NR	Diabetic patients with ESRD	Preference-based measures (review)	Diabetes + ESRD: 0.48 (95% CI 0.25 to 0.71)
Nafees 2014[409]	UK	100 general public	NR	NR	Patients with CHF and CKD (post hospital discharge)	TTO	CHF + CKD: 0.78 (SD 0.21)

CHF, chronic heart failure; HD, haemodialysis; HUI, Health Utilities Index; IQR, interquartile range; NR, not reported; PD, peritoneal dialysis; SD, standard deviation; SE, standard error; SF-36, Short Form Questionnaire-36 items.
a All non-UK studies identified after secondary screening; not part of the original search.

TABLE 43 Included studies from the AKI and CKD cost searches (all UK studies)

First author and year	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Reported costs
AKI costs						
Kerr 2014[323]	148,226 admissions	Adults	NR	AKI in critical care/ general ward	Retrospective analysis of hospital records/database; economic Markov model. NHS perspective; 2010/11 prices	Annual inpatient cost (England) £380M (excluding critical care), £1.02B (including critical care). Cost of post-discharge care £179M
Kolhe 2014[331]	576	Mean 76	57	AKI in ICU/ward	Retrospective analysis of hospital records/database	Inpatient cost of AKI: overall £3748, AKIN 1 £3233, AKIN 2 £3206, AKIN 3 £4287, requiring RRT £8405, no RRT £3504
Paterson 2013[332] and 2014[333]	366	Median 64	56	AKI requiring dialysis in ICU	Retrospective single-centre before-and-after study	Low-volume RRT resulted in an annual 12% cost saving of £27,000 vs. high-volume RRT
CKD costs						
Baboolal 2008[371]	NA	NR	NR	Patients requiring dialysis	Multicentre retrospective cost analysis comparing dialysis modalities. NHS perspective; 2006 prices	Annual costs: automated PD £21,655, CAPD £15,570, hospital HD £35,023, satellite HD £32,669, home HD £20,746
Black 2010[372]	NA	Mean 72	44	CKD (KDOQI) stages 1–4, excluding diabetes	Economic model comparing CKD referral strategies. NHS perspective; 35-year time horizon; 2006/7 prices	Annual CKD costs: CKD £344–492 (stage 3a–4), CKD + CVD £572–93. 35-year costs from £11,798 (current care) to £13,487 (referral at CKD stage 3a)
Chamberlain 2014[373]	370	Mean 47–53	62–66	Renal transplant recipients	Retrospective multicentre study of 3-year post-transplant costs. NHS perspective; 2010 euros (£1 = €1.16)	3-year costs: GFR < 15: €19,230; 15 ≤ GFR ≥ 30: €16,215; 30 ≤ GFR ≥ 45: €13,943; 45 ≤ GFR ≥ 60: €9169; GFR ≥ 60: €8475
Grün 2003[374]	171	Mean 77	67	Patients requiring dialysis	Prospective cohort study of post-transplant costs. Societal perspective; 1995 prices	Annual cost £22,740 (95% CI £21,467 to £24,015). Cost to social services £522 (2.3% of overall cost)
[a]Iqbal 2014[375]	NR	NR	NR	Patients requiring dialysis	Budget impact model to assess early cannulation arteriovenous grafts (ecAVGs) vs. tunnelled central venous catheters (TCVSs). Hospital perspective; price year NR	6-month treatment costs: £5882 (TCVS) vs. £4954 (ecAVG) per patient
[a]Joseph 2010[376]	NA	NR	NR	Patients requiring dialysis	Economic model to assess increasing the percentage of patients receiving home dialysis. NHS perspective; price year NR	Projected annual cost of current care in 2013 £35,048 vs. £31,584 for increased percentage of patients receiving home dialysis

First author and year	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Reported costs
Kadam 2013[377]	60,660	All ≥ 40	36–39	CKD + diabetes and CHF	Retrospective database analysis to assess the cost of CKD. NHS secondary care perspective; price year NR	3-year A&E costs: CKD no diabetes £80, CKD + diabetes £105, CKD no CHF £75, CKD + CHF £164. Hospital costs: £2559, £3642, £2477 and £5344 respectively
Kent 2015[370]	7246	Mean 63	64	CKD stages 1–5 ± CVD and diabetes	Randomised multicentre clinical trial to assess the cost of CKD. Median follow-up 4.9 years; NHS perspective; 2011 prices	Annual hospital costs: CKD stages 1–3B £403, CKD stage 4 £393, CKD stage 5 £525, maintenance dialysis (year 1) £18,986, dialysis ongoing £23,326, kidney transplant (year 1) £24,602, transplant (ongoing) £1148
Kerr 2014[323]	NA (national databases)	NR	NR	CKD stages 3–5	Retrospective database analysis and economic model to assess the cost of CKD. NHS perspective; 2009/10 prices	Annual cost £1.44–1.45B. Mean cost £27,000 on dialysis, £235 not on dialysis, £12,000 transplant recipients. Excess strokes and myocardial infarctions cost £174–8M per annum
Kirby 2001[378]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Economic Markov model to assess the cost-effectiveness of HD vs. CAPD strategies. Lifetime horizon; hospital perspective; 1999 prices	Monthly costs: HD £827–923, CAPD £905, minor complications £2.50 (HD) and £8 (CAPD), major complications £1799 (HD) and £2111 (CAPD). Total cost: HD £63,370–79,478 (depending on scenario), CAPD £65,061–76,426
Komenda 2012[379]	NA	NR	NR	Patients requiring dialysis	Economic model to assess the home HD service. Payer perspective; 2010 US dollars	Home HD year 1: in-centre HD US$45,374, conventional home HD US$46,218, frequent home HD US$57,898. Subsequent years: US$45,034, US$37,762 and US$49,442 respectively
[a]Liu 2013[380]	NA	NR	NR	Patients requiring dialysis	Budget impact model to assess dialysis modalities. NHS perspective; 5 year horizon; price year NR	Current 5-year cost: £4,380,678,000. Increasing prevalence of PD by 1.5% or 3% per year projected to save £18.5–63.6M
Liu 2014[381]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Budget impact model to assess increasing the percentage of patients receiving home dialysis. NHS perspective; 5-year horizon; 2013/14 prices	Base-case 5-year per-patient cost: £23,187. In scenarios 5-year budget impact of increasing the percentage of patients receiving home dialysis ranged from a saving of £572 (£2.5%) to an increase in costs of £1043 (4.5%)
Liu 2015[382]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Economic model to assess high-dose HD vs. conventional in-centre HD. Lifetime horizon; UK NHS perspective; 2013/14 prices	Lifetime discounted cost: base case (100% in-centre HD) £191,207; 100% high-dose in-centre HD £299,920

continued

TABLE 43 Included studies from the AKI and CKD cost searches (all UK studies) (*continued*)

First author and year	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Reported costs
McEwan 2006[383]	NA	NR	NR	Renal transplant recipients	Economic model to assess sirolimus vs. tacrolimus for the prevention of graft failure. 20-year post-transplant horizon; NHS perspective; 2003 prices	Sirolimus £62,120, tacrolimus £75,265–81,972 (depending on data profiles used)
[a]McEwan 2010[384]	879	NR	NR	Renal transplant recipients	Retrospective single-centre study of post-transplant costs. NHS perspective; price year NR	3-year costs: > 60 ml/minute/1.73 m^2 group £497, 30–60 ml/minute/1.73 m^2 group £1323, < 30 ml/minute/1.73 m^2 group £1448
[a]McEwan 2012[385]	NA	NR	NR	CKD requiring dialysis or transplantation	Economic model to assess the impact of graft survival time on transplantation cost-effectiveness. NHS perspective; 10-year time horizon	10-year cost: remain on dialysis £394,379, functioning graft £118,049. 4-year graft survival was cost saving
Mowatt 2003[386]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Economic model of home vs. in-centre HD. 5-year horizon; NHS perspective; 2001/2 prices	Annual costs: hospital HD £22,246, satellite HD 21,264, home HD 19,470. 5-year costs: £42,722, £46,001 and £41,250 respectively
Muduma 2014[387]	Hypothetical $n = 100$	NR	NR	Renal transplant recipients	Budget impact model of Prograf vs. Advagraf to prevent graft failure. 5-year horizon; NHS perspective; 2012/13 prices	5-year cost: Advagraf £29,328, Prograf £33,061. Cost saving of £375,000 for 100 patients
Muduma 2014[388]	NA	Model starting age = 45	NR	Renal transplant recipients	Economic model of immunosuppressents to prevent graft failure. 25-year horizon; NHS perspective; 2012/13 prices	25-year costs: Prograf £127,661, Advagraf £116,733, belatacept £116,733, ciclosporin £127,187, sirolimus I £103,896, sirolimus II £103,896
Muduma 2014[389]	NA	NR	NR	Renal transplant recipients	Budget impact model to assess Adgraf vs. Prograf for graft failure. NHS perspective; 5-year horizon; 2012/13 prices	5-year costs: Advagraf £26,941, Prograf £30,356
[a]Muduma 2015[390]	Hypothetical $n = 100$	NR	NR	Renal transplant recipients	Economic model of Prograf vs. Advagraf to prevent graft failure. NHS perspective; 2014 prices	Mean 5-year costs: Prograf £40,974, Advagraf £45,836 (cost saving of £4862)
Neil 2009[391]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Budget impact model of dialysis costs. NHS perspective; 2007 prices	Projected 5-year cost of shift to HD : PD ratio of 70 : 30: £133M
NICE 2011[392]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Economic model of dialysis settings and modalities. NHS perspective; 2008/9 prices	Monthly costs: hospital HD £2919, satellite HD £2722, home HD £1439, transplantation £10,250–13,627, transplant maintenance £583. 10-year costs: base £130,681, HD centred £136,146, PD £120,752

First author and year	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Reported costs
NICE 2011[393]	NA	NR	NR	Patients requiring dialysis (with ESRD)	Budget impact model of dialysis modalities. NHS perspective; 2011/12 prices	Unit costs: home HD £23,271, hospital HD £22,916, satellite HD £22,916, CAPD 17,411, APD 21,071. 5-year impact (1% PD increase per year): saving of £4,087,000
Oates 2012[394]	78	Mean 68	55	Patients requiring dialysis	Prospective costing study to assess online haemo-diafiltration (OL-HDF) vs. high-flux HD. Perspective and price year NR	Dialysis session costs: high-flux HD £25.56, OL-HDF £24.78. Weekly drug costs 3 months prior to starting and 12 months post starting: high-flux HD £21 and £24 respectively, OL-HDF £16 and £21 respectively
[a]Pollock 2013[395]	NA	NR	NR	Renal transplant recipients	Budget impact model to assess Prograf vs. Advagraf to prevent graft failure. 5-year horizon; perspective NR; 2012/13 prices	5-year cost per patient: Advagraf £29,290, Prograf £33,032. Total cost saving of £3742
[a]Pollock 2013[396]	NA	NR	NR	Renal transplant recipients	Budget impact model of Prograf vs. Advagraf to prevent graft failure. Perspective NR; 5-year horizon; 2012/13 prices	5-year cost per patient: Advagraf £26,958, Prograf £30,379. Total cost saving £3421
Popat 2014[397]	45	Mean 48–54	38–71	Renal transplant recipients	Prospective single-centre study to assess the cost of IL2Mab vs. antithymocyte globulin (ATG) to prevent graft failure. Perspective and price year NR	Average cost in year after transplant: IL2Mab £18,929, ATG £14,904 ($p = 0.002$)
Roderick 2005[398]	736	Mean 56–67	53–66	Patients requiring dialysis	Cost study to assess renal satellite units (RSUs) vs. main renal units (MRUs). Health service and patient perspective; 2000/1 prices	Total annual (or since starting dialysis) cost of all hospitalisations: MRU mean range £31–138 (depending on assumptions), RSU £35–125
[a]Sun 2010[399]	NA	NR	NR	Renal transplant recipients	Economic model to assess the cost of renal graft failure post transplant. Investment perspective	1-year cost of renal graft failure approximately £58,847. Post graft failure cost £28,179
Thompson 2013[400]	Hypothetical $n = 1000$	Mean 58	61	CKD (stages 3–4) not on dialysis	Economic model to assess sevelamer vs. calcium carbonate. NHS perspective: lifetime horizon: 2011 prices	Model costs: HD session £161, PD session £53.15. Lifetime costs: calcium carbonate £46,117, sevelamer £83,399
Treharne 2014[401]	Hypothetical $n = 100$	NR	NR	Patients requiring dialysis (with newly diagnosed ESRD)	Economic model to assess the cost-effectiveness of increasing the percentage of patients receiving PD. NHS perspective; 5- and 10-year horizon; 2013/14 prices	Current care (22% PD): 5-year horizon £96,307, 10-year horizon £133,339. Cost savings for increasing uptake to 39% PD: £3180 and £4102 respectively; cost savings for increasing uptake to 50% PD: £5238 and £6758 respectively

A&E, accident and emergency; CAPD, continuous ambulatory peritoneal dialysis; CHF, congestive heart failure; CVD, cardiovascular disease; GFR, glomerular filtration rate; HD, haemodialysis; KDOQI, Kidney Disease Outcomes Quality Initiative; NA, not applicable; NR, not reported; PD, peritoneal dialysis.
a Abstract only.

TABLE 44 Included studies for the AKI and CKD risk searches

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
AKI studies							
Abosaif 2005[343]	UK	183	Mean 65	68	AKI in ICU on first day. Excluded patients with CKD or renal transplant	Retrospective review of medical notes. AKI patients compared with a randomly selected control group with decrease in eGFR of < 25%	AKI incidence: risk 60/183 (33%), injury 56/183 (31%), failure 43/183 (23%), control group 24 (13%). CVVH in ICU (percentage requiring): 39%, 28%, 50%, 58%, 4%. ICU mortality: 38%, 50%, 75% and 17% respectively. 6-month mortality: 43%, 54%, 86% and 25% respectively
Alassar 2012[344,345]	UK	79	Mean 84	59	AKI (Valve Academic Research Consortium criteria) after transcatheter aortic valve implantation. Excluded patients with CKD or on dialysis	Single-centre observational study	ICU AKI incidence: stage 1 9/79, stage 2 1/79. AKI resolved in 9/10 patients before hospital discharge. No patients required RRT in hospital and LOS was not affected by AKI; 3/10 patients died within 1 year vs. 13/79 for the total cohort
Ali 2007[346]	UK	5321 (37 received RRT)	NR	NR	Patients receiving RRT in hospital	Retrospective analysis of population hospital records	37 (8%) AKI patients received RRT; 23 (62%) had first RRT in the ICU, 13 (35%) in the renal unit and one in a surgical high-dependency unit; 21 (57%) patients died within 6 months vs. 5 (45%) of patients with AKI on CKD who received RRT
[a]Barnes 2014[347]	UK	169	NR	83	AKI (AKIN criteria) in ICU within 48 hours after off-pump CABG surgery	Retrospective analysis of hospital records	Incidence 46/169 (27.2%); 50% AKIN stage 1, 30% stage 2, 20% stage 3. Mean ICU LOS was 2.3 days for all patients and 4 days for patients requiring CRRT

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Bastin 2013[348]	UK	1881	> 16; mean 68	71	AKI (AKIN, RIFLE, KDIGO) after cardiac surgery with CPB. Excluded patients on chronic dialysis or who died within 24 hours of surgery	Retrospective analysis of hospital records	(AKIN and KDIGO) no AKI 1394 (74.1%), stage 1 317 (16.9%), stage 2 34 (1.8%), stage 3 136 (7.2%); 122/1881 (6.5%) required RRT in hospital. ICU LOS (median): no AKI 1 day, stage 1 2 days, stage 2 4 days, stage 3 13 days; hospital LOS (median): 7, 9, 14 and 24 days respectively; hospital mortality: 4 (0.3%), 1 (0.3%), 0, 19 (14%) respectively
Baudouin 1993[367]	UK	35	Mean 56	74	Patients requiring RRT (continuous venovenous haemofiltration) after CPB surgery	Retrospective database/ records review	35/1300 (2.7%) patients required RRT in the ICU. Mean time from surgery to RRT was 8 days and mean time spent on RRT was 8 days; 3/9 ICU survivors died in hospital after ICU discharge
Bedford 2014[349]	UK	19,940	Mean 62–76	45–52	AKI (AKIN) in hospital. Excluded patients receiving chronic dialysis, maternity patients and day-case admissions	Retrospective analysis of hospital database	Mean ICU LOS: no AKI 3.0 days, AKIN 1 4.4 days, AKIN 2 4.5 days, AKIN 3 7.3 days; 77/588 (13.1%) patients with stage 3 AKI received RRT in hospital; 16/77 RRT patients remained on RRT 90 days post discharge
Bhandari 1996[366]	UK	1095 (cardiac 139)	NR	NR	AKI (acute uraemic emergency with serum creatinine ≥ 600 µmol/l and/or requiring dialysis) post cardiac surgery	Retrospective review of medical notes	Post-cardiac surgery severe AKI subgroup: 90-day survival 54 (38.8%), 90-day dialysis dependence 2 (1.4%)
[a]Brown 2014[350]	UK	2297 (306 with AKI)	NR	58	AKI requiring diffusive haemodialysis (CRRT) in ICU. Mixed non-surgical and surgical patients	Analysis of hospital records	319/2297 (13.9%) patients admitted to the ICU required CRRT. Mean LOS (days): RRT patients 13, all patients 8.2. Mortality at hospital discharge was 56% for RRT patients and 20% for all patients

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
[a]Chakkalakal 2013[338]	UK	71	NR	70–81	Patients in ICU with creatine kinase > 5000 w/l	Retrospective analysis of hospital records	AKI incidence: 39/71 (55%); 19 (27%) patients required RRT. Hospital mortality: no AKI 9%, AKI stages 1–3 25%, RRT 79%. ICU mortality: RRT 79%, no RRT 15%
Challiner 2014[351]	UK	745	NR	55	AKI (RIFLE, AKIN, AKIB) in ICU. Excluded maternity patients, admissions of < 24 hours, and patients on chronic dialysis	Retrospective audit	AKI incidence: RIFLE: risk 3 (2.9%), injury 5 (10.4%), fail 4 (20%); AKIN: stage 1 5 (4.3%), stage 2 4 (11.8%), stage 3 5 (23.8%). ICU AKI mortality 6/26
de Mendonça 2000[352]	16 countries including the UK	1411	> 12; median 63–57		AKI (serum creatinine ≥ 300 µmol/l and/or urine output < 500 ml/day) in ICU. Excluded patients with ICU stay of < 48 hours, a history of RRT or had had an elective operation	Prospective, multicentre, observational cohort analysis	AKI incidence: 348/1411 (24.7%). Median ICU LOS (days): AKI 7, no AKI 4. ICU LOS was the same for survivors and non-survivors. ICU mortality: AKI 149/348 (42.8%), no AKI 199/1068 (18.6%); hospital mortality: AKI 49.1%, no AKI 17.7%
Grayson 2003[353]	UK	5132	50% < 65; 39% 65–74; 11% > 75	75	AKI after cardiac operation involving CPB. Excluded patients with pre-existing significant renal impairment (serum creatinine > 200 mol/l)	Retrospective cohort analysis	AKI hospital incidence: 151 (2.9%); 105/151 patients with ARF did not require dialysis
[a]Hurtado-Doce 2014[354]	UK	512	Median 54	71	AKI after cardiac surgery and requiring CRRT	Retrospective analysis of hospital records	60/512 (12%) patients required CRRT for AKI. Mortality: all 23/512, no RRT 17/452, RRT 6/60
[a]Karmali 2015[355]	UK	262	NR	NR	AKI after CABG surgery using CPB (ONCAB, *n* = 131) or off-pump (OPCAB, *n* = 131). Excluded dialysed patients	Retrospective analysis of hospital records	AKI incidence: all 20/262 (7.6%), OPCAB 14/131 (10.7%), ONCAB 19/131 (14.5%). RRT in ICU: all 15/262 (5.7%), OPCAB 6/131 (4.6%), ONCAB 9/131 (6.9%). Mean ICU LOS (days): OPCAB 1.96, ONCAB 2.49

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Kerr 2014[323]	UK	NR	Adults (age NR)	NR	AKI in hospital with ICU subgroup. Chronic RRT patients excluded from hospital data but not identifiable in HES	Retrospective database (HES) and records analysis and economic decision model	Mean LOS: no AKI 0.05 days, stage 1 0.17 days, stage 2 0.31 days, stage 3 1.57 days, all AKI 0.35 days. Ratio vs. no AKI: stage 1 2.60 days, stage 2 5.61 days, stage 3 18.2 days, all AKI 4.32 days
[a]Khawaja 2012[337]	UK	249	Mean 83–82	62	AKI (modified RIFLE score ≥ 2) after transcatheter aortic valve implantation. Excluded patients with history of RRT	Retrospective review of medical records	AKI in ICU: 89 (35.7%); 30-day mortality: AKI 13.5%, no AKI 3.8%. Mortality at mean follow-up (338 days): AKI 40.4%, no AKI 19.4% ($p < 0.001$)
Kirwan 2015[356]	UK	5544	Median 64–66	78–82	AKI in ICU requiring RRT. Excluded patients with known CKD, ESRD or transplant in the last 10 years	Retrospective review of hospital records	781/5544 (14%) ICU admissions received RRT; 22/261 (8.4%) RRT survivors died within 3 months post hospital discharge; 7/261 commenced RRT within 3 months post discharge
Kolhe 2008[341]	UK	276,731 (17,326 with severe AKI)	Mean 63.2	66	Severe AKI (serum creatinine ≥ 300 µmol/l and/or urea ≥ 40 mmol/l) in first 24 hours of ICU admission. Excluded patients with a history of RRT or an ICU stay of < 8 hours	Retrospective review of hospital records	AKI incidence: 6.3% (17,326/276,731). Median ICU LOS (days): AKI survivors 4.1, AKI non-survivors 2.0, whole cohort survivors 1.7, whole cohort non-survivors 2.0; median hospital LOS (days): 31, 8, 16 and 9 respectively
Kolhe 2014[331]	UK	576	Mean 76	57	Primary or secondary diagnosis of AKI in hospital according to *International Classification of Diseases*, 10th Edition (ICD-10) codes	Retrospective database and activity records analysis	26 (4.5%) AKIN stage 3 patients required RRT in the ICU. AKI patients who needed RRT had a longer hospital LOS stay than those who did not need RRT: 16.7 vs. 10.3 days
[a]Kolic 2013[336]	UK	282	Median 50	68	AKI and CKD in the ICU with an ICU stay of > 5 days	Retrospective review of hospital records	180/282 (64%) patients had AKI in the ICU; 36/282 (12.8%) to 25/282 (8.9%) had CKD depending on the definition of CKD used

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
[a]Kourliouros 2009[342]	UK	1072	NR	NR	AKI after CABG surgery	Retrospective cohort study	Incidence of AKI in the ICU: 175/1072 (16%)
Metcalfe 2002[357]	UK	51	Median 71.4	65	Patients requiring RRT in hospital (either AKI or AKI on CKD)	Prospective observational study	23/34 (67.6%) patients with AKI had RRT in the ICU. Hospital LOS: median 19 days. At 90 days: recovered: AKI cohort 8 (23.5%), AKI on CKD 3 (16.5%). Mortality: AKI 25 (73.5%), AKI on CKD 12 (67%), CKD 4 (11%), all 41 (46%)
Noble 2001[363]	UK	612	Mean 57	61	AKI requiring RRT and mechanical ventilation for respiratory failure in the ICU	Retrospective database review and telephone interviews	ICU median LOS: AKI 9.6 days, no AKI 2 days, AKI survivors 12 days, AKI non-survivors 8.3 days. Hospital mortality: 64.1% (392/612)
Ostermann 2000[361]	UK	2337	Mean 65	Female-to-male ratio from 4 : 14 to 5 : 16	AKI (urine output $\leq$ 479 ml/24 hours or $\leq$ 159 ml/8 hours, serum urea $\geq$ 35 mmol/l, serum creatinine $\geq$ 300 mmol/l) after surgery with CPB	Prospective observational study compared with historical control subjects	47/2337 (2.0%) patients needed CVVH vs. 2.7% from historical data; 21/39 (53.8%) patients vs. 74% in the historical data died in the ICU. Hospital mortality: current, 53.8% vs. historical, 83%. Hospital mean LOS: survivors 53 days vs. non-survivors 17.3 days. Duration of CVVH (days): survivors 11 vs. non-survivors 12.7
Ostermann 2007[362]	UK and Germany	41,972	Mean 61	64	AKI (RIFLE) in the ICU. Excluded patients on dialysis at baseline	Retrospective database analysis	AKI incidence: risk 17.2%, injury 11%, failure 7.6%. ICU mortality: no AKI 5%, risk 14.7%, injury 36.5%, failure 47.6%. Hospital mortality: 8.4%, 20.9%, 45.6% and 56.8% respectively. Mortality odds ratio: risk 1.40, injury 1.96, failure 1.59

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Paterson 2013[332] and 2014[333]	UK	366	Mean 64–66	56–66	Patients receiving RRT in the ICU. Excluded patients receiving dialysis for CKD at baseline and interhospital ICU transfers	Retrospective before-and-after study of high-volume vs. low volume RRT	Days on RRT for survivors: high-volume RRT 12, low-volume RRT 8. ICU RRT mortality: high-volume RRT 55 (29%), low-volume RRT 61 (34%). Hospital mortality: high-volume RRT 77 (41%), low-volume RRT 75 (42%). Death post-ICU discharge: high-volume RRT 22 (12%), low-volume RRT 14 (8%)
Prescott 2007[358]	UK	809	> 15; median 65–72	61	Patients requiring RRT (either AKI or AKI on CKD) in the ICU or renal ward. Excluded patients requiring RRT for ESRD or with renal transplants	Prospective observational study	600 patients had AKI, 209 had AKI on CKD. Median days of RRT: AKI 5, AKI on CKD 8; 30% of AKI and 20% of AKI on CKD patients died within 10 days of starting RRT. Mortality at 90 days: AKI 50%, AKI on CKD 43%
Prowle 2014[335] and 2014[359]	UK	700	Median 46–51	Range 62–70	AKI (KDIGO) in the ICU with an ICU stay of > 5 days and patient surviving to hospital discharge. Excluded patients with new or pre-existing ESRD and transplant recipients	Retrospective analysis of hospital records	AKI incidence: 66% (459/700); stage 1 218 (31%), stage 2 75 (11%), stage 3 166 (24%). 121/700 (17.3%) patients received RRT. ICU median LOS (days): all 12, no AKI 8, stage 1 11.5, stage 2 11, stage 3 12. Hospital median LOS (days): no AKI 28, AKI 22
Ricci 2008[369]	Worldwide including the UK	71,000 (8398 with relevant outcome)	NR	NR	AKI (RIFLE) in the ICU	Systematic review with meta-analysis	RR (vs. no AKI) for mortality in the ICU: risk 1.77, injury 2.35, failure 4.63. RR (vs. risk): injury 1.32, failure 2.33. RR (vs. injury): failure 1.74
Saratzis 2015[339]	UK	149	Mean 69	89	AKI (AKIN and KDIGO) ≤ 48 hours post cardiac surgery (elective endovascular abdominal aneurysm repair). Excluded patients with ESRD or on dialysis at baseline	Prospective cohort study	AKI incidence: 28 (18.8%); stage 1 25, stage 2 3. Post-discharge mortality: AKI 32.1%, no AKI 1.7%. AKI hazard ratios: mortality 0.035, cardiovascular morbidity 0.021

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Susantitaphong 2013[334]	Worldwide	888,604 (ICU), 164,333 (cardiac)	Mean 23–80	NR	AKI (KDIGO) in ICU or post cardiac surgery	Literature review of large cohort studies with meta-analysis	AKI incidence in the ICU: 31.7% (95% CI 28.6% to 35.0%), post cardiac surgery: 24.3% (95% CI 20.4% to 28.8%). AKI ICU mortality: 33.1% (95% CI 29.8% to 36.6%), post cardiac surgery: 8.3% (95% CI 6.6% to 10.4%)
[a]Syed 2011[360]	UK	373	Adults (age NR)	NR	AKI stage 1 (AKIN) in ICU	Retrospective review of medical records to assess the impact of early oxygen delivery	ICU mortality for AKI stage 1 23.8%; hospital mortality for all 31.6%. No significant difference in hospital mortality between high and low oxygen monitoring groups. 48/249 (19.3%) patients with no monitoring progressed to AKI stage 3
Thomson 2014[340]	UK	264	Mean 70	Female-to-male ratio 1 : 3	AKI after CABG surgery and/or aortic valve surgery in cardiothoracic ICU	Prospective observational study to assess the impact of goal-directed therapy (GDT)	AKI incidence at day 3: GDT group 6.5%, control group 19.9%
Tsang 1996[368]	UK	48	Mean 65	71	AKI requiring continuous hemofiltration after cardiac surgery	Retrospective database/ records review plus telephone interviews	319/2297 (13.89%) patients admitted to the ICU required CRRT. Mean LOS: RRT patients 13, all patients 8.2. Mortality at hospital discharge: RRT patients 56%, all patients 20%
Uchino 2005[364]	23 countries including the UK	29,269 (1738 with AKI; 52 UK patients)	Median 67	64	Patients with AKI [urine output < 200 ml/12 hours and/or a marked blood urea nitrogen level > 84 mg/dl (30 mmol/l)] or treated with RRT in the ICU	Prospective observational study	AKI incidence: 1738/29,269 (5.8%), UK subgroup 20.6%; 1260 (4.2%) were treated with RRT in the ICU, 52% died in the ICU, 60.3% died in hospital (73.1% in the UK subgroup). Dialysis dependence at hospital discharge: 13.8% for AKI survivors
Uchino 2007[365]	23 countries including the UK	1006	Median 66	66	Patients with AKI requiring CRRT in the ICU. Excluded patients on dialysis	Prospective observational study	ICU mortality: 555/1003 (55.3%). Hospital mortality: 641/999 (64.2%); 85.5% were dialysis independent at hospital discharge

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
CKD studies							
[a]Anwar 2012[411]	UK	548	NR	NR	Renal transplant recipients with at least 3 years of follow-up data	Single-centre observational study	56/548 (10.2%) patients were on dialysis within 5 years post transplantation
[a]Babu 2014[412]	UK	155 (80 in CKD group)	Mean 61–69	NR	Patients with CKD and primary prevention cardiac resynchronisation therapy devices	Single-centre observational study	Mean survival time: CKD 59.7 months, no CKD 81.2 months. CKD was an independent predictor of sustained ventricular arrhythmia
Balupuri 2000[442]	UK	47	16–60	NR	Renal transplant recipients either from heart-beating donors (HBDs) or non-heart-beating donors (NHBDs)	Single-centre prospective study	In phase I, 19/21 (90.5%) HBD transplants were successful; in phase II (including non-HBDs), 5/11 (45.5%) transplants were successful; in phase III (non-HBDs including other departments), 12/13 (92.3%) transplants were successful
[a]Bevins 2013[413]	UK	201	NR	NR	CKD stage 4	Retrospective analysis	Over a median follow-up of 1483 days, 60/201 patients progressed to RRT (i.e. ESRD)
Chamberlain 2014[373]	Europe	3181 (370 in the UK)	Mean 47–53	62–66	Renal transplant recipients. Excluded multiorgan transplants	Retrospective multicentre study	Database results: over 3 years post-transplant outcomes for UK: delayed graft function 22.4%, acute rejection 37%, graft failure 10%, stroke 0%, death 1.9%. Questionnaire results: 29.9%, 20.6%, 11.5%, 2% and 2.7% respectively
[a]Chan 2011[414]	UK	1288	Mean 46	62	Renal transplant recipients	Cohort analysis	15-year patient and allograft survival was 84.6% and 66.8% respectively; 13/70 deaths were from malignancy

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
[a]Cherukuri 2014[415]	UK	504	NR	NR	Renal transplant recipients	Prospective cohort analysis	Transplant recipients who were vitamin D deficient had worse overall survival (77% vs. 92%) and death censored graft survival (89% vs. 96%) than those with normal vitamin D levels
Cherukuri 2010[416]	UK	94	Mean 63	69	Incident patients starting dialysis and on dialysis for at least 90 days	Prospective observational cohort study	39/94 (41%) patients died during the study period, mostly from vascular disease (39%) or sepsis/infection (33%); 56% ($n = 22$) of deaths occurred in the first year
CKD Prognosis Consortium 2010[444]	International including the UK	105,872	NR	NR	General population cohorts	Systematic review and meta-analysis	Compared with an eGFR of 95 ml/minute/1.73 m^2, adjusted hazard ratios for all-cause mortality were 1.18 for 60 ml/minute/1.73 m^2), 1.57 for 45 ml/minute/1.73 m^2 and 3.14 for 15 ml/minute/1.73 m^2). Similar findings were recorded for cardiovascular mortality
CKD Prognosis Consortium 2011[445]	International including the UK	21,688	NR	NR	Kidney disease cohorts	Systematic review and meta-analysis	Below an eGFR of 45 ml/minute/1.73 m^2, a 15-ml/minute/1.73 m^2 drop in eGFR was significantly associated with mortality (hazard ratio 1.47) and ESRD (hazard ratio 6.24)
Coresh 2014[417]	International	1.7 million	Mean 51–74	49–80	Mixed cohorts with and without CKD. Excluded patients with ESRD at baseline	Meta-analysis of studies from an international consortium consisting of 50 cohorts with > 1000 participants	A change of –57% in estimated GFR over 2 years was associated with adjusted hazard ratios for ESRD of 32.1 at lower eGFRs (< 60 ml/minute/1.73 m^2) and 57.2 at higher eGFRs (≥ 60 ml/minute/1.73 m^2). Mortality HRs were 3.7 and 3.8 respectively

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Drey 2003[451]	UK	405,000	NR	NR	Detected CKD in a general population cohort	Retrospective cohort study	Annual incidence of CKD: 1701 per million population with a median age of 77 years and male-to-female ratio of 1.6. CVD was the most common cause of death (46%); 4% were accepted for RRT
Ekberg 2009[448]	International including the UK	1645	Median 47	65	Renal transplant recipients with low-to-normal immunological risk	Randomised trial	Biopsy-proven acute rejection: 25% at 12 months, 26% at 24 months, 27% at 36 months; death censored graft survival: 94%, 92% and 91% respectively; uncensored graft survival: 92%, 89% and 88% respectively; patient survival: 97%, 96% and 95% respectively
[a]Farrugia 2013[418]	UK	19,103	NR	NR	Renal transplant recipients	Retrospective database analysis	2085/19,103 of patients died, 376 (18.0%) because of malignancy
[a]Favi 2015[419]	UK	639	NR	NR	Renal transplant recipients	Single-centre observational study to assess polyomavirus-associated nephropathy (PVAN)	Death-censored graft loss rates: PVAN 42%, no viraemia 14%
Fellstrom 2005[420]	International including the UK	1052	Mean 50	65.2	Renal transplant recipients	RCT (but assessed placebo arm only in this analysis)	Over 5–6 years of follow-up: 54/1052 patients experienced cardiac death and 65/1052 experienced non-cardiac death and 66/1052 had definite myocardial infarction
Gansevoort 2011[443]	International including the UK	845,125 general population and 173,892 high risk	Mean 26.4–66.9	39.5–100	General population and CKD high-risk cohorts	Systematic review and meta-analysis	Hazard ratios for ESRD at eGFRs of 60, 45 and 15 ml/minute/1.73 m^2 (vs. 95 ml/minute/1.73 m^2) in the general population cohort analysis: 3.69, 29.3 and 454.9 respectively

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Ghazanfar 2010[449]	UK	201	Mean 37.4	Male-to-female ratio 6 : 1	Renal transplant recipients (living donors)	Retrospective analysis	Graft survival at 1, 2 and 5 years post transplant: 93%, 89% and 87%, respectively, for multiple arteries; 94%, 91% and 89%, respectively, for single arteries. Patient survival rates at 1, 2 and 5 years post transplant: 97%, 93% and 92%, respectively, for multiple arteries; 95%, 94% and 91%, respectively, for single arteries. Mean graft and patient survival rates at 10 years were 71% and 79%, respectively, for multiple arteries and 77% and 83%, respectively, for single arteries
Hamed [a]2013[421] and [a]2014[422]	UK	1090	NR	NR	Renal transplant recipients	Single-centre observational study	52/1090 (4.8%) patients experienced early graft loss and had an 8.5 times increased risk of death, with 1-year survival less than that for those on the waiting list (76.9% vs. 88.8%); 5-year survival in the early graft loss group was better than that for waiting list patients (69.3% vs. 51.4%). Retransplantation after early graft loss resulted in 1-year graft survival of 86.7%
Humar [a]2009[423] and [a]2010[424]	UK	318	NR	NR	High-risk renal transplant recipients	International RCT	1-year rates of acute rejection (17.2% vs. 11%) and graft loss (1.8% vs. 1.9%) were comparable between the 100-day and the 200-day prophylaxis groups respectively. Patient survival was 100% and 97% respectively

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Jardine 2005[425]	UK	1052	Mean 50	65.2	Low-risk renal transplant recipients	RCT (but assessed placebo arm only in this analysis)	Over a mean 65.3-month follow-up, 54/1052 patients experienced cardiac death and 65/1052 experienced non-cardiac death and 66/1052 had a definite myocardial infarction
Karim 2014[426]	UK	19,103	Median 45	61	Renal transplant recipients, excluding multiorgan transplants	Retrospective database linkage and review (population cohort analysis)	2085/19,103 patients died over a median follow-up of 4.4 years. Repeat transplantations occurred in 635 recipients over the 11-year period
Kent 2015[370]	International including the UK	7246	Mean 63	64	CKD ± CVD; CKD stages 1–3: 1494; CKD stage 4: 2228; CKD stage 5 no dialysis: 1017; on dialysis: 2498	Randomised prospective trial	Vascular deaths per patient-year: CKD stages 1–3b 36 (0.6%), CKD stage 4 92 (1%), CKD stage 5 86 (2.2%), CKD stage 5 + dialysis 235 (2.5%); non-vascular deaths per patient-year: 1.6%, 2.5%, 3.8% and 4.9% respectively; kidney transplant in current period: 0.2%, 1.6%, 5.4% and 6.7% respectively; kidney transplant in earlier period: 0.1%, 1.4%, 8.5% and 2.5% respectively; dialysis initiated in current period: 1.3%, 6.2%, 18.2% and 0.2% respectively; dialysis from earlier period: 0.7%, 6.9%, 33.8% and 80.6% respectively
[a]Krishnan 2013[427]	UK	13,167	NR	64	Renal transplant recipients	Retrospective database analysis	857 (18%) patients suffered rejection and 205 (3%) patients died
[a]Mark 2010[428]	UK	199	NR	NR	Patients with CKD stage 5, with contrast cardiovascular magnetic resonance imaging and assessed for renal transplant	Cohort analysis	Over a median follow-up of 61.6 months there were 61 (30.7%) deaths, of which 36 (59%) were cardiovascular deaths

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Marks 2012[447]	UK	3414	Median 78.6	44.2	CKD (67% stage 3, 30% stage 4, 2% stage 5), excluded patients receiving RRT	Retrospective cohort study (case note review)	At 6 years' follow-up, 170 (5%) patients had initiated RRT (with 77 subsequently dying), 59% died without initiating RRT and 36% were alive without RRT. Adjusted incident rate ratios for initiating RRT: CKD stage 4 vs. 3: 5.60, stage 5 vs. 3: 38.10; adjusted incident rate ratios for all-cause mortality: 1.41 and 1.55 respectively
Moore 2011[429]	UK	2763	Mean 46	60	Renal transplant recipients surviving at least 12 months post transplant and all treated with ciclosporin mircroemulsion	Retrospective database analysis	In a development data set, 196/2763 (7%) patients died and 225 (8%) experienced transplant failure. In a validation data set, 44/731 (6%) patients died and 101 (14%) experienced transplant failure
Nath 2015[430]	UK	1095	Mean 27–48	40–66	Obese patients receiving single organ renal transplantation with multiple renal arteries	Retrospective single-centre analysis	1-year graft survival: all 996/1095 (91%), underweight 30/33 (91%), normal weight 378/403 (94%), overweight 358/394 (91%), obese 230/265 (87%). Patient 1-year survival: survival for all 99%, all 97%, underweight 99%, normal weight 99%, overweight 98% and obese 99% respectively
NHS Blood and Transplant 2015[450]	UK	8608	NR	NR	Renal transplant recipients/ patients on transplant waiting list	Kidney Activity Report (registry analysis)	Over 1 year (2014/15), of 8608 patients on the kidney transplant waiting list, 5713 (66%) remained on the list, 2183 (25%) were transplanted, 491 (6%) were removed from the list and 221 (3%) died. For patients transplanted in 2010–13, 1-year graft survival was 94% and 1-year patient survival was 96%

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Raymond 2007[431]	UK	106,366	Mean 58	44.5	Community population with at least one serum creatinine measurement, retrospectively assigned to CKD stages	Retrospective database analysis	Annual mortality increased with CKD stage: stages 1 and 2 1.9%, stage 3A 6.4%, stage 3B 11.1%, stage 4 16.5%, stage 5 20.6%. RR for mortality: 4.0, 8.3, 16.2 and 43.5 for CKD stage 3A, 3B, 4 and 5 respectively. This impact reduced with age
Renal Association 2014[410]	UK	6680	NR	NR	RRT patients	Analysis of registry data	After 5 years' follow-up, of 5034 patients on HD, 31% remained on dialysis, 16% had a transplant and 51% died. Of 1297 patients on PD, 29% remained on dialysis, 37% had a transplant and 33% died. Of 349 patients on the transplant waiting list, 4% were on dialysis, 92% remained on the transplant waiting list and 5% died
Robinson 2012[432]	International including the UK	24,525	Mean 61–63	54–58	Patients with ESRD for > 180 days, receiving haemodialysis	Prospective cohort study	5849/24,525 patients died over 42,174 patient-years of follow-up (rate 0.14 per year)
Roderick 2009[433]	UK	15,336	Median 80.2	39	Older patients (75+ years) with CKD in the community	Clinical trial	In the first 2 years of follow-up, adjusted hazard ratios for all-cause mortality for eGFR bands 45–49, 30–44 and < 30 ml/minute/1.73 m^2 vs. > 60 ml/minute/1.73 m^2 were 1.13, 1.69 and 3.87, respectively, for males and 1.14, 1.33 and 2.44, respectively, for females
[a]Seitz 2015[434]	UK	14,027	NR	NR	First-time renal transplant recipients	Retrospective database analysis	Median time to rejection was 126 days in the alemtuzumab group and 35 days in the non-alemtuzumab group

continued

TABLE 44 Included studies for the AKI and CKD risk searches (*continued*)

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Shabir 2014[435]	UK	651	Mean 44.2–52.4	60–63	Renal transplant recipients alive at 12 months post transplantation	Cohort analysis	Development cohort: for patients alive at 12 months post transplant, 31/651 died from 1–5 years post transplant and 91/651 had transplant failure. Validation cohort: for patients alive at 12 months post transplant, 58/787 (7.4%) died from 1–5 years post transplant and 62/787 (7.9%) had transplant failure
Taal 2007[436]	UK	35	Median 63.8	60	CKD stages 4 and 5 not yet on dialysis. Excluded patients with renal transplantation or on dialysis	Retrospective analysis of longitudinal study	After a median of 12.4 months, 22/35 (63%) patients with stage 4/5 CKD had commenced dialysis
Thomson 2007[437]	UK	263	Median 66.7	51.3	Patients receiving haemodialysis in a renal unit	Retrospective analysis	Over an 18-month follow-up period, 65/263 (24.7%) patients had died; 15 underwent renal transplantation and one recovered renal function
Udayaraj 2009[438]	UK	2770	Median 58	58	Patients with ESRD receiving PD therapy at 180 days from start of RRT	Retrospective analysis of UK Renal Registry	1104/2770 patients died over a median follow-up of 3.7 years
van der Velde 2011[446]	International including the UK	266,975	NR	NR	High-risk cohorts	Systematic review and meta-analysis	Risk for all-cause mortality was not associated with an eGFR between 60 and 105 ml/minute/1.73 m^2 but increased at lower levels. Hazard ratios at eGFRs of 60, 45 and 15 ml/minute/1.73 m^2 were 1.03, 1.38 and 3.11, respectively, compared with an eGFR of 95 ml/minute/1.73 m^2. There were similar findings for cardiovascular mortality

First author and year	Country	*n*	Age (years)	Sex male (%)	AKI/CKD status	Methods	Key risk results
Vivek 2010[439]	UK	126	Mean 46–55	Male-to-female ratio from 16 : 16 to 56 : 38	Renal transplant recipients	Retrospective cross-sectional study	Over a mean of 91 months' follow-up, 35 (27.8%) patients died. Cardiac deaths accounted for 12% of all deaths
Wen 2014[440]	UK	1,130,472	NR	NR	General population cohort	Meta-analysis	In Asian, whites and black patients, compared with an eGFR of 90–104 ml/minute/1.73 m^2, the hazard ratios for eGFR 45–59 ml/minute/ 1.73 m^2 were 1.25, 1.09 and 1.33 for all-cause mortality, 1.59, 1.40 and 1.44 for cardiovascular mortality and 27.6, 11.2 and 4.05 for ESRD respectively
Woo 2002[441]	UK	434	NR	62.9	Renal transplant recipients	Longitudinal cohort study	Age (hazard ratio 1.03), diabetes (hazard ratio 2.72), smoking (hazard ratio 1.81) and family history of premature CVD (hazard ratio 2.17) were independent risk factors for patient survival. Acute rejection (hazard ratio 2.38), smoking (hazard ratio 1.48) and age (hazard ratio 1.04) were independent predictors of graft failure

AKIB, acute kidney injury biomarkers; ARF, acute renal failure; CRRT, continuous renal replacement therapy; CVD, cardiovascular disease; CVVH, continuous venovenous haemodialysis; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HD, haemodialysis; HES, Hospital Episode Statistics; LOS, length of stay; NR, not reported; PD, peritoneal dialysis; RR, relative risk.
a Abstract only.

TABLE 45 UK AKI utility studies identified from additional searches of utility databases

First author and year	*n*	Age (years)	Sex male (%)	Methods	Utility
Latimer 2013[462]	123	All > 80	0–32	RCT of shock-absorbing floor for hospital falls. EQ-5D data collected 3 months post discharge for patients treated on a general ward	Mean utility for the 'no fall' group 0.38 (vs. 0.27–0.36 for fall categories)
Hernández 2014[460]	286	Median 59–60	60	Trial assessing ICU follow-up programmes. EQ-5D data collected at baseline (shortly after ICU discharge) and 6 and 12 months post discharge	Mean utility: baseline: 0.44 standard care vs. 0.49 for increased follow-up; 6 months: 0.62 vs. 0.63 respectively; 12 months: 0.60 vs. 0.58 respectively
Cuthbertson 2010[461]	300	Median 61	59	Prospective cohort study to assess long-term quality of life post ICU admission. EQ-5D data were collected at 1, 2.5 and 5 years after ICU admission. Scores were compared with those of hypothetical age- and sex-matched control subjects	Mean utility: 12 months post ICU admission: 0.666 vs. 0.82 in matched cohort; 2.5 years' follow-up: 0.701 vs. 0.818 in matched cohort; 5 years' follow-up: 0.677 vs. 0.817 in matched cohort

The database searches identified 689 records, with 496 remaining after removal of duplicates (*Figure 31*). In total, 37 relevant reviews and papers were initially identified. Within these 37 studies, four key recurring interventions were identified: early RRT, early nephrologist involvement, AKI e-alert systems and intravenous administration of alkaline phosphatase. Based on a review of the literature findings and expert consultation, evidence on the impact of early RRT was deemed to be currently contentious and this intervention was therefore not explored further. For the remaining interventions citation tracking was conducted to identify UK primary ICU studies. In total, eight primary studies[463–470] were included for data extraction and are summarised in *Table 46*.

Evidence on the impact of e-alert systems was mixed, with the largest identified study finding no impact.[463] Alkaline phosphatase appears to be a potentially effective treatment for AKI but as of yet there are limited data to support use of this intervention in practice. The evidence on the impact of early nephrologist consultation was deemed to be of most relevance for this study as this can reasonably be assumed to represent a proxy for the non-specific bundle of early AKI treatments that patients would access as a result of biomarker-led early diagnosis. All of the four identified studies in this area reported some impact of early consultation on patient mortality and the largest study ($n = 1096$) reported a significant impact of early consultation on the incidence of AKI, with an adjusted odds ratio of 0.71 (95% CI 0.53 to 0.95; $p = 0.02$).[464]

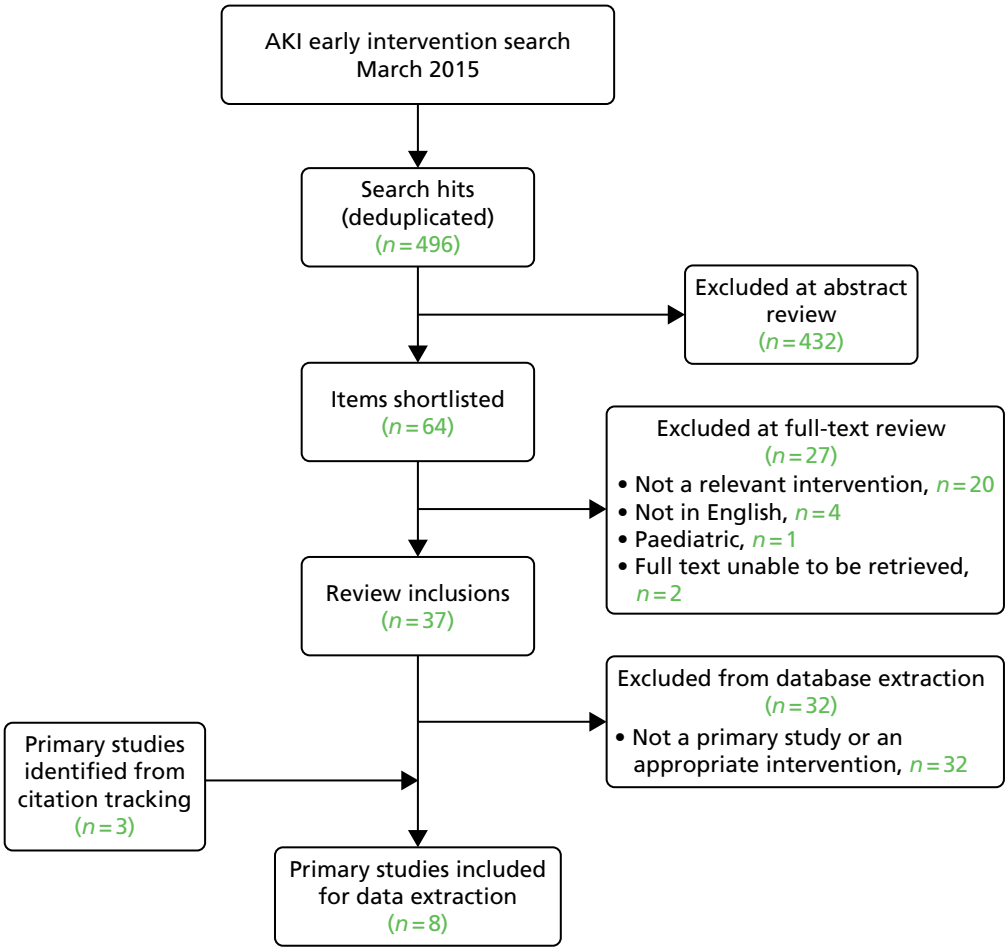

FIGURE 31 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the AKI early intervention search.

TABLE 46 Summary of early AKI intervention studies in the ICU in the last 5 years

First author and year	Country	*n*	AKI status	Methods	Key results
Early nephrologist involvement					
Flores-Gama 2013[464]	Mexico	1096	AKI (RIFLE/AKIN) within 7 days of cardiac surgery in the cardiac ICU	Retrospective time series analysis of impact of nephrology on-demand vs. nephrology on-site (i.e. integrated into the daily ICU team) on renal recovery	Patients treated with nephrology on-site had a lower incidence of AKI (25.7% vs. 31.9%; adjusted OR 0.71) and in-hospital mortality for severe AKI (34.1% vs. 55.9%; adjusted OR 0.33) and higher renal recovery at hospital discharge (61.0% vs. 35.3%; adjusted OR 3.57) than patients treated with nephrology on-demand. No differences in ICU stay or mechanical ventilation
Costa e Silva 2013[465]	Brazil	366	AKI (increase of ≥ 50% in baseline serum creatinine level according to the RIFLE risk stage) in the ICU and length of ICU stay > 48 hours	Prospective observational study to assess the impact of early (< 48 hours from AKI diagnosis day) vs. delayed (≥ 48 hours after AKI diagnosis) nephrology consultation	Of 53.6% who had a nephrologist consultation, those with a delayed consultation had a higher rate of hospital mortality (adjusted OR 3.39), increased dialysis dependence (adjusted OR 3.25), a longer ICU stay (19 vs. 13.5 days), a longer time on mechanical ventilation support (16.5 vs. 10 days) and a longer time from diagnosis to dialysis (7 vs. 2 days)
Ponce 2011[466]	Brazil	148	AKI (AKIN) in the ICU	Prospective observational study of the impact of delayed nephrologist consultation (≥ 48 hours after AKI diagnosis)	Of patients who received a consultation, 29 received an early consultation and 48 received a late consultation. Delayed consultation was associated with increased ICU mortality (65.4% vs. 88.2%, adjusted OR 1.32)
Mehta 2002[467]	USA	215	AKI in the ICU and hospital. AKI defined according to blood urea nitrogen and serum creatinine criteria	Prospective observational study to assess the impact of delayed (≥ 48 hours) nephrology consultation	Delayed consultation was associated with increased in-hospital mortality (adjusted OR 2.0), length of hospital stay (median 19 vs. 16 days) and length of ICU stay (17 vs. 6 days)
Electronic e-alerts					
Wilson 2015[463]	USA	1393	Patients in hospital (including ICU) with stage 1 or above KDIGO AKI	Single-blind, parallel-group RCT of a text-based e-alert system. Patients were stratified by medical vs. surgical admission and ICU vs. non-ICU location	The e-alert system did not affect patient clinical outcomes (change in creatinine level, dialysis and death at 7 days post randomisation)
Colpaert 2012[468]	Belgium	951	AKI (RIFLE) in the ICU	Prospective time series analysis of a telephone alert system. Three	More patients in the alert group received intervention within 60 minutes of alert

TABLE 46 Summary of early AKI intervention studies in the ICU in the last 5 years (*continued*)

First author and year	Country	*n*	AKI status	Methods	Key results
				consecutive study phases: a 1.5-month pre-alert control phase, a 3-month intervention phase and a 1.5-month post-alert control phase	(28.7% vs. 7.9% and 10.4% in the pre- and post-alert control groups respectively) and received fluid therapy, diuretics and vasopressors ($p < 0.001$) and more patients in the alert group returned to a baseline kidney function within 8 hours of a 'risk' alert ($p = 0.048$). There was no impact on ICU length of stay, use of RRT or mortality
Alkaline phosphatase					
Pickkers 2012[469]	The Netherlands	36	Patients with severe sepsis or septic shock and AKI (AKIN) in the ICU	Prospective RCT to assess the impact of intravenous infusion of alkaline phosphatase within 48 hours of AKI onset	Creatinine clearance (baseline to day 28) was significantly higher in the treated group (from a mean of 50 ± 27 to 108 ± 73 ml/minute vs. from a mean of 40 ± 37 to 65 ± 30 ml/minute for placebo). Reductions in RRT requirement and duration were not significant
Heemskerk 2009[470]	The Netherlands	36	Patients with bacterial infection, more than two systemic inflammatory response syndrome criteria and < 12 hours end-organ dysfunction onset in the ICU	A multicentre RCT to assess treatment with an initial bolus intravenous injection of alkaline phosphatase followed by continuous infusion over the following 23 hours and 50 minutes	Over 28 days, mortality was 24% in the alkaline phosphatase group vs. 36% in the placebo group; RRT use was 24% in the alkaline phosphatase group vs. 36% in the placebo group. In patients with AKI, serum creatinine levels tended to decrease over the 2 days after the start of alkaline phosphatase treatment ($p = 0.12$), whereas there was a non-significant increase in the placebo group ($p = 0.49$)

OR, odds ratio.

Acute kidney injury registry data

The Epidemiology of AKI in ICU study[471] is an ongoing prospective observational international study with the primary aim of identifying the incidence and prevalence of AKI among critically ill patients. The study includes in the first instance an initial 'screening period' during which data on patient age, sex, weight, baseline creatinine level, daily creatinine level and urine output are collected over 7 days from patient admission to ICUs across participating sites. As a result this study provides a registry of daily individual patient data for patients experiencing AKI in the ICU. If a patient is found to meet AKI criteria within the screening period, informed consent is pursued to enable further research-specific activity. All patients admitted to the ICU are eligible for inclusion, with the exception of patients on chronic haemodialysis or peritoneal dialysis within the past 12 months, those with a functioning kidney transplant and prisoners. Currently, six hospitals in England have enrolled or begun enrolling patients, with the highest number of enrolled patients to date coming from the Leeds Teaching Hospitals NHS Trust (LTHT).

For the AKI-Diagnostics study, in July 2015 data were requested from the AKI registry on patients treated at LTHT. Data were provided on 60 patients who experienced AKI in the ICU, 13 of whom were in the ICU post cardiac surgery. An overview of the baseline characteristics of these patients is provided in *Table 47*. A summary of patients' ICU and hospital length of stay and mortality is provided in *Table 48*.

Data on these patients were used to determine patient ICU daily status across the 10 possible AKI hospital period health states: AKI KDIGO S0, S1, S2, S3 and S3 + RRT, discharged to hospital ward, discharged to hospital ward + RRT, discharged home, discharged home + RRT and mortality. The daily statuses were used to derive daily Dirichlet transition probabilities between the health states for the model baseline AKI cohort. When AKI status could not be determined because of missing serum creatinine or urine output data, the closest observed AKI status value was carried forwards or backwards, as required. An adjustment of +0.01 was applied to all values to enable Dirichlet estimation in the presence of zero values.

TABLE 47 Leeds Teaching Hospitals NHS Trust AKI registry data: patient characteristics

Characteristic	AKI cohort ($n = 60$)	AKI post cardiac surgery ($n = 13$)
Mean (SD) age (years)	68 (13)	71 (7)
Male (%)	77	92
Type of ICU (%)		
General	71.7	0.0
Cardiac	21.7	69.2
Surgical	6.7	30.7
Admission diagnosis (%)		
Trauma	1.7	–
Cardiac surgery	21.7	100
Vascular surgery	3.3	–
Other surgery	10.0	–
Sepsis/septic shock	13.3	–
Intoxication	0.0	–
Neurological diagnosis	3.3	–
Cardiac diagnosis	18.3	–
Respiratory diagnosis	18.3	–
Nephrological diagnosis	0.0	–
Gastrointestinal diagnosis	10.0	–
Haematological diagnosis	0.0	–
Oncological diagnosis	0.0	–
Endocrine diagnosis	0.0	–
Not reported	0.0	–
Surgery status (%)		
Emergency	18.3	7.7
Elective	35.0	92.3
None	46.7	0.0
Not reported	0.0	0.0

SD, standard deviation.

TABLE 48 Leeds Teaching Hospitals NHS Trust AKI registry data: length of ICU and hospital stay and mortality

Variable	ICU	Hospital (from ICU admission)
***AKI cohort* (n = *60*)**		
LOS < 30 days, % (*n*)	92 (55)	80 (48)
LOS < 60 days, % (*n*)	98 (59)	92 (55)
LOS < 90 days, % (*n*)	100 (60)	95 (57)
LOS (days), minimum, maximum	0, 65	0, 175
Mean LOS (days)	8	19
Median LOS (days)	4	10
Mortality, % (*n*)	53 (32)	59 (35/59[a])
***AKI cohort post cardiac surgery* (n = *13*)**		
LOS < 30 days, *n*/*N* (%)	11/13 (85)	10/13 (77)
LOS < 60 days, *n*/*N* (%)	13/13 (100)	11/13 (85)
LOS < 90 days, *n*/*N* (%)	13/13 (100)	12/13 (92)
LOS (days), minimum, maximum	2, 39	4, 123
Mean LOS (days)	10	25
Median LOS (days)	6	11
Mortality, % (*n*)	8 (*n* = 1)	15 (2)

LOS, length of stay.
a One patient had missing hospital discharge data, and was excluded from the hospital mortality calculation. For the hospital LOS, the last known date of contact in the hospital (the patient consent date) was used as a proxy for the hospital discharge date.

A summary of the patients' maximum ICU AKI status is provided in *Table 49* and a summary of patients' daily AKI status is provided in *Figure 32* [note that, because of the size of the daily Dirichlet transition matrices (10 × 10 × 90), these are not reported].

Intensive care unit and hospital discharge and mortality data were also used to derive Kaplan–Meier survival curves for ICU length of stay (*Figure 33*) and survival (*Figure 34*), which were used to calculate daily discharge and mortality probabilities for the no AKI cohort by applying a relative risk (RR) (RR 0.30 for ICU and hospital mortality and RR 0.54 for ICU length of stay) to the AKI cohort survival curves (see *Model parameters* for more details).

TABLE 49 Leeds Teaching Hospitals NHS Trust AKI registry: maximum AKI status over first 7 days in the ICU

Maximum ICU AKI status	% (*n*)
AKI S1	50 (30)
AKI S2	20 (12)
AKI S3	7 (4)
AKI S3 + RRT	23 (14)

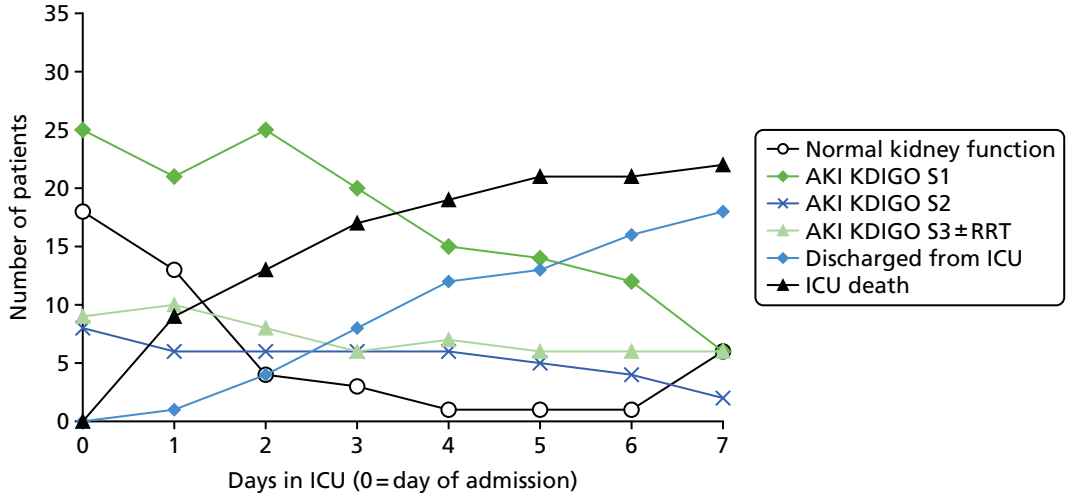

FIGURE 32 Leeds Teaching Hospitals NHS Trust AKI registry: daily ICU AKI status over 7 days from admission.

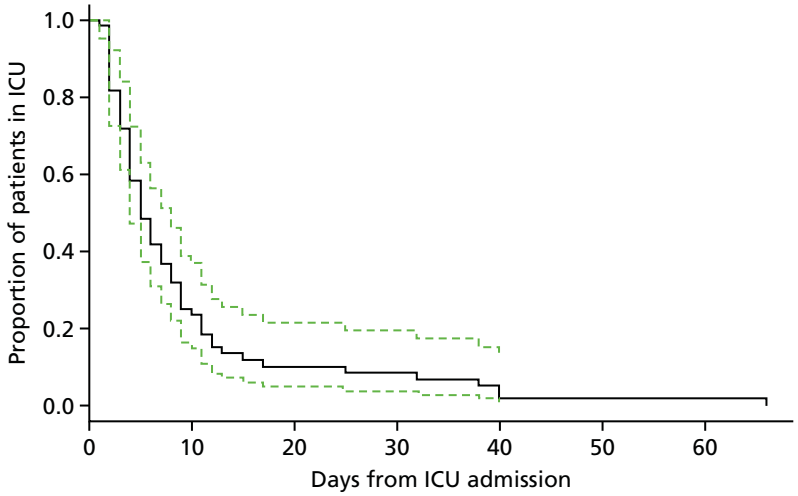

FIGURE 33 Leeds Teaching Hospitals NHS Trust AKI registry: Kaplan–Meier survival curve for AKI cohort ICU length of stay.

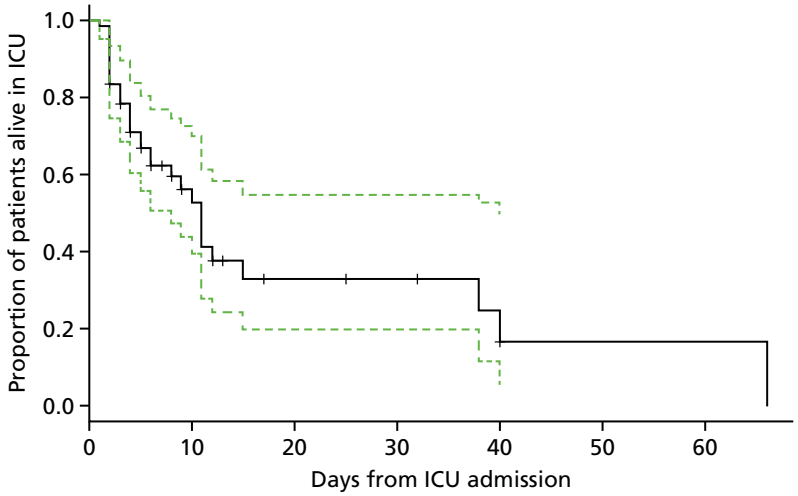

FIGURE 34 Leeds Teaching Hospitals NHS Trust AKI registry: Kaplan–Meier survival curve for AKI cohort ICU survival.

Model parameters

A summary of the model base-case parameters is provided in *Table 50*.

Hospital period parameters

For the hospital period of the model, the proportion of patients expected to experience AKI in the ICU (either on arrival or after) was derived from the worldwide systematic review (2004–12) of large cohort studies[334] identified from the AKI risks literature search (see *Model parameter literature review*), which reported a pooled incidence rate across 41 studies ($n = 888,604$) for KDIGO AKI of 31.7% (95% CI 28.6%

TABLE 50 Economic model base-case parameters

Parameter	Base-case value	SD	Distribution	Source
Patient characteristics				
Starting age (years) of ICU cohort	61	–	Fixed	LTHT AKI registry data[471]
Proportion male	0.70	–	Fixed	LTHT AKI registry data[471]
Risks: hospital period				
Proportion who have or develop AKI in the ICU (AKI cohort)	0.317	0.018	Beta	Susantitaphong *et al.*[334]
Proportion who have or develop AKI in the ICU post cardiac surgery (secondary analysis)	0.243	0.021	Beta	Susantitaphong *et al.*[334]
AKI cohort: end day 1 with normal kidney function (as proportion of total ICU population)	0.095	0.019	Dirichlet	LTHT AKI registry data[471]
AKI cohort: end day 1 with AKI S1	0.132	0.021	Dirichlet	LTHT AKI registry data[471]
AKI cohort: end day 1 with AKI S2	0.042	0.014	Dirichlet	LTHT AKI registry data[471]
AKI cohort: end day 1 with AKI S3	0.037	0.013	Dirichlet	LTHT AKI registry data[471]
AKI cohort: end day 1 on RRT	0.011	0.007	Dirichlet	LTHT AKI registry data[471]
AKI cohort: daily transition probabilities for AKI cohort states (days 1–90)	–	–	Multiple Dirichlet	LTHT AKI registry data[471]
AKI cohort: ICU mortality (used to inform no AKI cohort mortality only)	Survival curve	–	NA (10,000 curve simulations)	LTHT AKI registry data[471]
AKI cohort: hospital ward (post ICU) daily mortality	0.009	0.003	Beta	LTHT AKI registry data[471]
No AKI cohort: RR for ICU and hospital mortality in no AKI cohort vs. AKI cohort	0.30	0.10	Log-normal	Model calibration using LTHT AKI registry data,[471] Susantiphong *et al.*,[334] Chakkalakal *et al.*,[338] de Mendonça *et al.*[352] and Ostermann and Chang[362]
AKI cohort: ICU length of stay (used to inform no AKI cohort discharge rates only)	Survival curve	–	NA (10,000 curve simulations)	LTHT AKI registry data[471]
No AKI cohort: RR for ICU stay in no AKI cohort vs. AKI cohort	0.542	0.15	Log-normal	de Mendonça *et al.*,[352] Prowle *et al.*,[335] Ostermann and Chang[362] and LTHT AKI registry data[471]

continued

TABLE 50 Economic model base-case parameters (*continued*)

Parameter	Base-case value	SD	Distribution	Source
No AKI cohort: probability discharged from ICU to hospital ward vs. home	0.484	0.06	Beta	LTHT AKI registry data[471]
No AKI cohort: daily probability discharged from hospital	0.089	0.03	Beta	LTHT AKI registry data[471] and Prowle *et al.*[359]
Post-discharge mortality	0.0003	1.33×10^{-5}	Beta	Lone *et al.*[457]
On RRT post-discharge mortality	0.0004	1.83×10^{-5}	Beta	Renal Association[472]
Utilities: hospital period				
In ICU	–0.402	0.20	Normal	Kind *et al.*[473] (Appendix B)
In hospital ward (post ICU)	0.44	0.31	1 – gamma	Hernández *et al.*[460]
Discharged (post ICU)	0.62	0.32	1 – gamma	Hernández *et al.*[460]
Decrement for dialysis dependence (any time point post ICU discharge)	0.11	0.02	Normal	Wyld *et al.*[402]
Daily costs: hospital period (£)				
Daily cost of ICU	1306	290	Log-normal	Department of Health[474]
Daily cost of hospital ward	304	111	Log-normal	Curtis and Burns (p. 111)[475]
Daily excess cost of AKI in hospital (any setting)	265	77	Log-normal	Department of Health[474]
Daily excess cost of dialysis in hospital (any setting)	691	1154	Log-normal	Department of Health[474]
Daily cost of discharged patient dialysis independent	17	0.52	Log-normal	Lone *et al.*[457]
Daily cost of discharged patient dialysis dependent (excess cost)	69	0.24	Log-normal	Kent *et al.*[370]
Utilities: follow-up period				
Post-discharge recovery (year 1)	0.67	0.28	1 – gamma	Cuthbertson *et al.*[461]
Post-discharge recovery (years 2–4)	0.70	0.281	1 – gamma	Cuthbertson *et al.*[461]
Post-discharge recovery (year 5 onwards, i.e. 'recovered')	0.68	0.301	1 – gamma	Cuthbertson *et al.*[461]
Successful kidney transplant	0.68	0.301	1 – gamma	Assumed equivalent to 'recovered'
CKD stages 1–4 (decrement from 'recovered')	0.02	0.03	1 – gamma	Wyld *et al.*[402]
ESRD no dialysis (decrement from 'recovered')	0.20	0.09	1 – gamma	Wyld *et al.*[402]
ESRD maintenance dialysis (decrement from 'recovered')	0.11	0.02	Normal	Wyld *et al.*[402]
Annual costs: follow-up period (£)				
Post-discharge follow-up (annual) year 1	6230	190	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 2	4010	156	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 3	3811	169	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 4	3618	182	Log-normal	Lone *et al.*[457]

TABLE 50 Economic model base-case parameters (*continued*)

Parameter	Base-case value	SD	Distribution	Source
Post-discharge follow-up (annual) year 5	3178	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 6	2739	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 7	2299	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 8	1860	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 9	1421	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 10	981	165	Log-normal	Lone *et al.*[457]
Post-discharge follow-up (annual) year 11+	542	165	Log-normal	Lone *et al.*[457]
Ratio for impact of AKI on follow-up costs	1.15	0.074	Log-normal	Lone *et al.*[457]
CKD stages 1–4 (additional cost)	579	56	Log-normal	Kent *et al.*[370]
ESRD no dialysis (additional cost)	760	69	Log-normal	Kent *et al.*[370]
ESRD maintenance dialysis year 1 (additional cost)	20,440	234	Log-normal	Kent *et al.*[370]
ESRD maintenance dialysis year 2+ (additional cost)	25,035	87	Log-normal	Kent *et al.*[370]
Functioning transplant year 1 (additional cost)	26,301	341	Log-normal	Kent *et al.*[370]
Functioning transplant follow-up years (additional cost)	1467	122	Log-normal	Kent *et al.*[370]
Annual risks: follow-up period				
Starting distributions	From hospital model end states	–	–	From end state distributions from hospital period model (10,000 simulations)
Follow-up period mortality year 1 (AKI and no AKI)	0.109	0.004	Beta	Lone *et al.*[457]
Follow-up period mortality years 2–5 (AKI and no AKI)	0.066	0.002	Beta	Lone *et al.*[457]
Background age- and sex-standardised mortality (applied in year 6 onwards)	Mortality table	–	Fixed	Office for National Statistics[476]
Baseline rate of CKD in post-ICU population	0.0044	–	–	Rimes-Stigare *et al.*[477]
RR of CKD in AKI cohort vs. no AKI cohort	7.6	1.25	Log-normal	Rimes-Stigare *et al.*[477]
CKD mortality (stages 1–4)	0.03	0.002	Beta	Kent *et al.*[370]
CKD to ESRD + dialysis	0.04	0.002	Beta	Kent *et al.*[370]
CKD to ESRD no dialysis	0.01	0.001	Beta	Kent *et al.*[370]
ESRD (CKD stage 5) no dialysis mortality	0.12	0.005	Beta	Kent *et al.*[370]

continued

TABLE 50 Economic model base-case parameters (*continued*)

Parameter	Base-case value	SD	Distribution	Source
ESRD no dialysis to transplant	0.09	0.004	Beta	Kent *et al.*[370]
ESRD no dialysis to ESRD + dialysis	0.18	0.006	Beta	Kent *et al.*[370]
ESRD remain on dialysis	0.784	0.006	Dirichlet	Renal Association[472]
ESRD + dialysis to transplant	0.062	0.004	Dirichlet	Renal Association[472]
ESRD + dialysis to death	0.154	0.006	Dirichlet	Renal Association[472]
Transplant success	0.979	0.008	Dirichlet	Renal Association[472]
Transplant failure (move to dialysis)	0.014	0.007	Dirichlet	Renal Association[472]
Transplant to death	0.007	0.004	Dirichlet	Renal Association[472]
Test parameters				
Proportion who arrive in the ICU with pre-existing AKI (S2 and above) and who are therefore not tested	0.066	0.017	Beta	Communication with LTHT (January 2015)
Cost of the Nephrocheck test (£)	71.27	–	Fixed	Communication with manufacturer and LTHT (January 2015)
Cost of the NGAL test	14.98	–	Fixed	Communication with manufacturer and LTHT (January 2015)
Cost of the cystatin C test	4.26	–	Fixed	Communication with manufacturer and LTHT (January 2015)
Cost of early AKI intervention as a result of a positive test result (£)	205	279	Log-normal	Department of Health[474]
RR for AKI risks as a result of early treatment	0.782	0.255	Log-normal	Flores-Gama *et al.*[464]
Nephrocheck test: sensitivity	0.90	–	Multivariate normal	Meta-analysis
Nephrocheck test: specificity	0.49	–	Multivariate normal	Meta-analysis
NGAL test (plasma): sensitivity	0.72	–	Multivariate normal	Meta-analysis
NGAL test (plasma): specificity	0.81	–	Multivariate normal	Meta-analysis
NGAL test (urine): sensitivity	0.70	–	Multivariate normal	Meta-analysis
NGAL test (urine): specificity	0.79	–	Multivariate normal	Meta-analysis
NGAL test (serum): sensitivity	0.92	–	Multivariate normal	Chen *et al.*[34]
NGAL test (serum): specificity	0.69	–	Multivariate normal	Chen *et al.*[34]
Cystatin C test (plasma): sensitivity	0.72	–	Multivariate normal	Meta-analysis
Cystatin C test (plasma): specificity	0.74	–	Multivariate normal	Meta-analysis
Cystatin C test (urine): sensitivity	0.68	–	Multivariate normal	Meta-analysis
Cystatin C test (urine): specificity	0.76	–	Multivariate normal	Meta-analysis
Cystatin C test (serum): sensitivity	0.76	–	Multivariate normal	Meta-analysis
Cystatin C test (serum): specificity	0.88	–	Multivariate normal	Meta-analysis

SD, standard deviation.

to 35.0%). For patients who experienced AKI in the ICU, the daily distribution and movement of patients between the AKI health states was derived using individual patient data obtained from the LTHT AKI registry (see *Acute kidney injury registry data*).

To determine the probability of ICU discharge and mortality in the no AKI cohort, RRs were applied to 10,000 simulations of the relevant survival curves from the AKI registry for the AKI cohort. For the probability of ICU discharge, the RR was determined by taking the mean ratio (0.542) of the median ICU length of stay for the no AKI group compared with the AKI group observed across three studies identified from the review, assuming a constant ratio over time.[349,352,359,362] The RR for ICU and hospital ward mortality was determined by model calibration, by setting the RR value such that the observed ratio of death for the AKI cohort compared with the no AKI cohort at day 10 in the model was equivalent to the mean ratio of ICU mortality (3.92) observed across three studies identified from the literature.[343,352,362]

Daily hospital costs were derived from published *NHS Reference Costs 2014 to 2015*[474] and Personal Social Services Research Unit (PSSRU) costs.[475] The daily cost of ICU (£1306) was determined by taking a weighted average of reported reference costs for critical care 'Non-specific general adult critical care patients predominate', across 0 to 6 organs supported (service code CCU01; Currency codes XC0[1–7]Z). The daily cost of the hospital ward was derived from the reported PSSRU cost for a non-elective inpatient short stay (£608), assuming that an average 'short stay' would be 2 days (i.e. daily cost £304). The daily excess cost of AKI in hospital (ICU or ward) was derived by taking the weighted average of reference costs for (long-stay) excess bed-days for non-elective inpatients with AKI either with or without interventions (service codes LA07 [H/J/K/L/M/N/P]). This cost was assumed to be independent of the stage of AKI (for S1–S3 without RRT). A further excess cost of RRT was applied to all RRT states, which was taken as the weighted mean of reported reference costs for critical care 'Renal Dialysis for Acute Kidney Injury' using either haemodialysis or peritoneal dialysis for patients aged 19 years and over (service code RENALAKI; currency codes LE0[1/2]A).

In the absence of any identified data on patient utilities while in the ICU, patient utility was assumed to be equivalent to the utility of an unconscious patient reported in the EQ-5D scoring manual (–0.402)[473] and to be independent of AKI status. As a result of the significant uncertainty around this parameter, it was included in the planned sensitivity analysis.

The utility of patients in the hospital ward and post-hospital discharge states was derived from a RCT[460] identified from the review of utility databases (see *Model parameter literature review*), which evaluated a nurse-led ICU follow-up programme compared with standard care for 286 patients treated across three UK hospitals between 2006 and 2007. In the model, hospital ward utility is assumed to be equivalent to the reported baseline standard care arm utility (0.44) and post-discharge utility is assumed to be equivalent to the reported 6-month post-discharge utility (0.62). As for the ICU health states, because of a paucity of data, health state utilities for those on the general ward and those discharged were assumed to be independent of AKI status. However, a utility decrement was applied for anyone receiving RRT (–0.11), assuming a value equivalent to the reported disutility associated with chronic dialysis from a recent meta-analysis, which pooled data from 226 studies reporting dialysis utilities.[402]

Follow-up period parameters

The starting distribution of patients across health states in the follow-up period of the model was taken from the end-state distribution of patients in the hospital period model. All patients in non-RRT health states were assumed to enter the relevant 'follow-up' state in the AKI or no AKI cohort follow-up model, whereas patients in the AKI cohort occupying a RRT health state at the end of the hospital period were assumed to transition to the CKD health state in the follow-up model. All patients who died in the hospital period transitioned to the corresponding 'dead' states in the follow-up period.

Post-discharge follow-up mortality and costs were derived from a recent large cohort study that provided 5-year follow-up mortality and hospital resource use data on 5259 patients surviving to hospital discharge after an ICU admission in Scotland.[457] After 5 years, mortality was assumed to return to population norm

levels, which were sourced from UK Office for National Statistics data.[476] From year 6 to year 10, follow-up costs were assumed to continue to decrease at the same annual rate observed in the Lone *et al.*,[457] study with a constant value of standard deviation (SD); for year 11 onwards, costs were assumed to remain at the level calculated in year 11. For follow-up costs in the AKI cohort, a factor of 1.15 was applied to the baseline follow-up costs for the first 5 years. This value was derived from the Lone *et al.*[457] study, using the reported RR of 5-year follow-up hospital admission rates (used to derive costs in the study) for patients who required RRT during their ICU stay. This was assumed to be an appropriate proxy for the expected additional follow-up costs in the AKI cohort compared with the no AKI cohort as a result of renal injury in the first 5 years. Beyond 5 years, costs were assumed to be equal between the two cohorts.

The risk of progressing to the CKD state from the AKI cohort follow-up state was derived from a recent cohort study of 97,782 patients from the Swedish intensive care register (2005–11),[370] which reported the incidence of CKD at 1 year post ICU discharge for AKI (6%) and no AKI (0.44%) survivors and the associated incident rate ratio (7.6). This additional risk was assumed to apply for the duration of the follow-up model (i.e. until death). Subsequent probabilities relating to progression from CKD to ESRD, renal transplantation and mortality were derived from the Renal Association[472] and the study by Kent *et al.*,[370] which reported information on kidney disease progression and costs for 7246 patients included in the Study of Heart and Renal Protection (SHARP) international randomised trial. This study was also used to derive the annual costs of the CKD, ESRD and transplant health states.

Follow-up utility was derived from a prospective longitudinal cohort study that reported patient EQ-5D scores at 12 months (0.66), 2.5 years (0.701) and 5 years (0.677) post ICU admission for 300 patients treated within a UK university hospital ICU. Follow-up utility in year 1 of the follow-up model was assumed to be equivalent to the reported 12-month utility; utilities in years 2–4 were assumed to be equivalent to the reported 2.5-year utility; and utility in year 5 onwards was assumed to be equivalent to the reported 5-year utility. The utility for someone with a successful kidney transplant was assumed to be equivalent to the follow-up utility for year 5 onwards. Utility decrements for CKD, ESRD and chronic dialysis were applied to the successful transplant state value, using decrement values reported in a previous systematic review and meta-analysis of quality of life measures relating to CKD treatment modalities.[402]

Test parameters

Test accuracy

Each test was assumed to be conducted on all patients arriving in the ICU without known AKI (KDIGO stages 2 and above). The proportion of patients arriving in the ICU with known AKI stage 2 or above (0.066) was estimated by communication with the LTHT (January 2015), who had previously requested these data from the Intensive Care National Audit & Research Centre (ICNARC) database.

Test accuracy (sensitivity and specificity) was based on the results of the AKI-Diagnostics systematic review and meta-analysis including papers on adult patients only (see *Chapter 3*). Using the pooled mean sensitivity and specificity values and variance–covariance matrices, test accuracies were determined by drawing from multivariate normal distributions to maintain parameter correlation, using the 'mvrnorm' function in the R 'MASS' package (version 3).[478] This effectively specifies that the logit sensitivity and specificity were generated from a bivariate normal distribution. When fewer than two papers were available to conduct a meta-analysis [i.e. for NGAL (serum) in the primary base-case analysis and Nephrocheck and cystatin C (plasma) in the post-cardiac surgery secondary analysis], sensitivity and specificity values were derived using the individual papers from the review (all tests had at least one paper for both the primary and the secondary analyses). For these three cases, because of a lack of reported data, variance–covariance values were assumed to be equivalent to the variance–covariance matrix from the meta-analysis of that specific test in the corresponding primary/secondary analysis. For example, for NGAL (serum) in the base case, the values for the test sensitivity and specificity variance–covariance matrix were assumed to be equivalent to those observed in the meta-analysis of NGAL (serum) in the post-cardiac surgery secondary analysis.

Using the multivariate normal distribution for test accuracy parameters can result in values > 1 (which are invalid) when the mean values are close to 1 and/or the variance around these parameters is large. In these cases, in the absence of any alternative methodology, affected distributions were truncated at 1. For most of the tests for which this occurred, the proportion of points on the distribution lying above 1 was minimal, with the exception of NGAL (serum) (*Table 51*). This is a limitation of the analysis and an area requiring future methodological research.

Test costs

Direct test costs were derived by personal communication with each of the test manufacturers (January 2015). Laboratory staff and hospital overhead costs were derived by consultation with laboratory scientists and managers at LTHT (January 2015). The number of tests required to be conducted per year per hospital laboratory ($n = 1253$) was estimated based on the total number of ICU admission at St James's University Hospital, Leeds, in 2015 ($n = 1341$) minus the proportion of patients expected to arrive with pre-existing moderate-to-severe AKI who would not be tested (6.5% of 1341 = 88). This was assumed to be broadly representative of the expected workload for a typical medium-sized NHS hospital laboratory.

A breakdown of each of the test costs is provided in the following sections.

Nephrocheck

Nephrocheck tests are currently provided by Astute Medical and Ortho Clinical Diagnostics (Raritan, NJ, USA; in partnership with Astute Medical). Nephrocheck can be run both on the Astute 140® Meter or using a high-throughput VITROS® platform. Currently, the evidence on the diagnostic accuracy of this test relates to its use on the Astute 140 Meter. In addition, there may be adoption barriers to using the VITROS platform because of the relative rarity of this platform in UK clinical laboratories; in particular, the recent trend in UK laboratories towards participation in managed service contracts is expected to result in limited opportunities for the utilisation of alternative platforms outside these contracts. It was therefore assumed in the model that the Astute 140 Meter would be used. Manufacturer-estimated costs, quoted in euros, were converted into pounds using an exchange rate of 0.84.[315]

The cost of the Nephrocheck test consists of the:

- kit cost:
  - kit cost = €1250 for 25 tests = €50 per test = £42 per test
  - liquid control kit = €120 (assumed one per kit) = €4.80 per test = £4.03 per test
  - kit paper roll = €2.90 (assumed one per kit) = €0.116 per test = £0.0974 per test
  - kit quality control and shipping costs included in the kit cost
  - total kit cost = £46.13

TABLE 51 Proportion of model test sensitivity and specificity values lying above 1 when using the multivariate normal distribution

Test	Population (primary/secondary analysis)	Proportion of points > 1 (%)	
		Sensitivity distribution	Specificity distribution
Cystatin C (urine)	ICU all-comers	00.42	00.01
	Post cardiac surgery	00.07	03.55
Cystatin C (serum)	ICU all-comers	00.15	00.00
NGAL (serum)	ICU all-comers	26.35	00.02
	Post cardiac surgery	11.35	07.10

- platform cost:
  - Astute 140 Meter platform acquisition cost (assumed one per laboratory) = €10,000 = £8400
  - platform maintenance for 5 years (assumed lifetime of platform) = €900 × 2 + €600 (cost of two 2-year warranties plus one 1-year warranty) = €2400 = £2016
  - platform external quality control device (assuming manufacturer-recommended four devices per year for 5 years) = €97 × 4 × 5 = €1940 = £1629.6
  - total platform cost (per test over 5-year lifetime) = £12,045.6/(5 × 1253) = £1.92 per test
- indirect costs:
  - staff cost per test [assumed 30 minutes (top of the band) band 6 biomedical scientist time for non-automated test (£9.03) + 20% for headroom] = £10.85
  - trust overheads per test (assumed to be 21% of the total test cost) = (£46.13 + £1.92 + £10.85) × 0.21 = £12.37
- total cost per Nephrocheck test = £46.13 + £1.92 + £10.85 + £12.37 = £71.26.

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin tests are provided by two companies, BioPorto and Abbott Architect. Abbott Architect provides a specific platform for its test, whereas the BioPorto test can be run on several testing platforms. The BioPorto NGAL test kit is currently the cheaper option of the two and was therefore used in the cost calculation (assuming that the NHS would generally opt for the cheaper test). It was assumed that the test would be run using a Siemens ADVIA® 1800 platform (Siemens, Camberley, UK) as this is already used within several NHS laboratories (as are the Abbott Architect platforms). As these platforms are already in place and provide a significant turnover of tests under existing maintenance contracts, no additional platform maintenance or external quality control costs were included. In the absence of any data to indicate otherwise, costs for NGAL urine, plasma and serum tests were assumed to be equivalent. The cost of the NGAL tests consists of the:

- kit cost:
  - kit cost = £3600 for 300 tests = £12.00 per test
  - kit quality control and calibration costs included in kit cost
  - shipping cost = £18.50 for 300 tests = £0.06 per test
- platform cost:
  - not applicable
- indirect costs:
  - staff cost per test [estimated cost of running automated assay using Genesys laboratory software (Daly City, CA, USA)] = £0.32
  - trust overheads per test (assumed to be 21% of the total cost) = (£12.06 + £0.32) × 0.21 = £2.60
- total cost per NGAL test = £12.00 + £0.06 + £0.32 + £2.60 = £14.98.

Cystatin C

Several companies provide cystatin C test kits and the test may be run on several platforms. For this cost calculation, we assumed that the Siemens test and the ADVIA® Chemistry XPT Platform would be adopted, as this is currently used at the LTHT. As for the NGAL test, no platform maintenance or external quality

control costs were applied and costs across the plasma, urine and serum tests were assumed to be equivalent. The cost of the cystatin C test consists of the:

- kit cost:
  - kit cost = £250.63 for 400 tests = £0.63 per test
  - kit quality control costs per test (assuming 12 kits per year) = (£63.89 × 12)/1253 = £0.61
  - kit calibration costs per test (assuming six kits per year) = (£400 × 6)/1253 = £1.92
  - shipping cost assumed to be included in the kit cost
- platform cost:
  - not applicable
- indirect costs:
  - staff cost (estimated using Genesys laboratory software) = £0.32
  - trust overheads (assumed to be 21% of the total cost) = (£0.63 + £0.61 + £1.92 + £0.32) × 0.21 = £0.73
- total cost per cystatin C test = £0.63 + £0.61 + £1.92 + £0.32 + £0.73 = £4.21.

Impact of early acute kidney injury Intervention

The impact of early AKI intervention [applied to patients with a TP test result and currently no AKI or early AKI (KDIGO stage ≤ 1) according to concurrent standard care tests] was derived from a Mexican study identified in the literature review of early AKI interventions.[464] This study assessed the impact of early nephrologist consultation in a group of 1096 patients within 7 days of cardiac surgery. The reported adjusted odds ratio (0.71) for AKI incidence was used to derive a RR, which was applied to all upwards AKI progressions from the S0 and S1 states and for mortality in the S3 + RRT state. This value was supported by independent consultation with the specialist advisory group.

Post-cardiac surgery subgroup population parameters

In the secondary analysis, alternative parameters specific to the post-cardiac surgery subgroup were adopted when possible (*Table 52*). When no post-cardiac surgery-specific evidence could be identified, parameter values were assumed to be equivalent to those used in the base-case analysis. It was assumed that the same patient pathway as adopted in the base case would apply for this subgroup.

For the estimation of AKI incidence, the same worldwide meta-analysis was used as in the base case,[334] which reported a pooled KDIGO AKI incidence across 42 studies ($n = 164{,}333$ patients) in post-cardiac surgery populations of 24.3% (95% CI 20.4% to 28.8%). To inform the relative rate of ICU mortality and ICU and hospital discharge between the AKI cohort and the no AKI cohort, a single retrospective study was identified from the review that reported mortality and length of stay outcomes by AKI status for 1881 patients undergoing cardiac surgery necessitating CPB.[348] Daily ICU costs were derived as a weighted mean of critical care *NHS Reference Costs 2014 to 2015* for 'Cardiac surgical adult patients predominate' services.[474]

For test accuracies, sensitivity and specificity values for NGAL and cystatin C were derived from the post-cardiac surgery meta-analysis results, using the same methodology as outlined in the base case. For Nephrocheck, only one relevant paper was identified from the review, which did not report information on the parameter correlation. For this case we assumed the same variance–covariance matrix as observed in the meta-analysis of Nephrocheck studies conducted in all-comer ICU populations.

TABLE 52 Economic model post-cardiac surgery population secondary analysis parameters

Parameter	Base-case value	SD	Distribution	Source
Risks: hospital period				
Proportion who have or develop AKI in the ICU	0.243	0.021	Beta	Susantitaphong *et al.*[334]
No AKI cohort: RR for ICU and hospital mortality in the no AKI cohort vs. AKI cohort	0.12	0.04	Log-normal	Model calibration using LTHT AKI registry data[471] and Bastin *et al.*[348]
No AKI cohort: RR for ICU stay in the no AKI cohort vs. AKI cohort	0.216	0.07	Log-normal	Bastin *et al.*[348]
No AKI cohort: daily probability discharged from hospital	0.117	0.04	Beta	LTHT AKI registry data[471] and Bastin *et al.*[348]
Daily costs: hospital period				
Daily cost of ICU (generic)	£1275	get	Log-normal	Department of Health[474]
Test parameters				
Nephrocheck: sensitivity	0.80	–	Multivariate normal	Meersch *et al.*[54]
Nephrocheck: specificity	0.83	–	Multivariate normal	Meersch *et al.*[55]
NGAL (plasma): sensitivity	0.61	–	Multivariate normal	Meta-analysis
NGAL (plasma): specificity	0.77	–	Multivariate normal	Meta-analysis
NGAL (urine): sensitivity	0.66	–	Multivariate normal	Meta-analysis
NGAL (urine): specificity	0.62	–	Multivariate normal	Meta-analysis
NGAL (serum): sensitivity	0.84	–	Multivariate normal	Meta-analysis
NGAL (serum): specificity	0.87	–	Multivariate normal	Meta-analysis
Cystatin C (plasma): sensitivity	0.61	–	Multivariate normal	Tziakas *et al.*[69]
Cystatin C (plasma): specificity	0.56	–	Multivariate normal	Tziakas *et al.*[69]
Cystatin C (urine): sensitivity	0.52	–	Multivariate normal	Meta-analysis
Cystatin C (urine): specificity	0.72	–	Multivariate normal	Meta-analysis
Cystatin C (serum): sensitivity	0.73	–	Multivariate normal	Meta-analysis
Cystatin C (serum): specificity	0.72	–	Multivariate normal	Meta-analysis

Summary of model assumptions

As with any economic evaluation, this study has limitations. Various simplifying assumptions were adopted in the analysis to produce an efficient and workable model. In particular:

- The model is limited to an evaluation of the three tests judged currently to be of the highest priority. Many other tests are available and may represent cost-effective alternatives. The results of the multiway incremental analysis should therefore be interpreted with caution, as not all relevant comparators have been included.
- The model considers only the use of one-off testing on entry to the ICU. Use of tests in a sequential or monitoring context have not been considered.
- The model considers adult all-comers to the ICU only; paediatric populations were excluded from the analysis.
- The model does not directly consider the case of AKI on top of CKD. The majority of evidence on the accuracy of the tests excludes patients with existing CKD and we have therefore not attempted to model these patients.

- The model does not allow for re-entry to the ICU or hospital once a patient has been discharged. In reality, it is expected that in the short term a (potentially significant) proportion of patients would re-enter the ICU or hospital because of worsening health post discharge. This would be expected to have a noticeable impact on the results only if the biomarkers are expected to have an impact on the rate of re-admission.
- The model does not allow for a hospital length of stay of > 90 days. Based on an analysis of the LTHT AKI registry data,[471] it is expected that up to 5% of patients with AKI may stay in hospital for > 90 days (but 0% in the ICU).
- Any difference between arms in the model in the downstream incidence of CKD is dictated by the proportion of patients ending the hospital period model in RRT states. As such, the model does not pick up the impact on CKD related to a reduced severity of AKI in terms of reduced rates of KDIGO S1–S3, or from a reduced duration of AKI. The impact of the tests on long-term CKD rates may be underestimated in this case.
- The impact of early AKI intervention on patients' risks of developing worse AKI in the model lasts for the whole hospital period (i.e. 90 days).
- It was assumed that if patients are dialysis independent/dependent on hospital discharge, then they remain dialysis independent/dependent for the remainder of the hospital period of the model.
- For the NGAL and cystatin C tests, diagnostic accuracy was determined by pooling data from studies using different cut-off point thresholds, because of the limited availability of data and reporting on alternative cut-off points. It is unclear, therefore, if these tests were to be adopted in practice, which cut-off point(s) should be used.
- The analysis does not include societal costs because of the limited availability of data. Both the length of the ICU/hospital stay and the risk of CKD may have significant impacts on patient costs and productivity losses. This is therefore a key area for future research.
- The secondary analysis of the subgroup of patients in the ICU post cardiac surgery is limited; only a few parameters were updated for this analysis based on data available from the literature reviews. In particular, the same ICU daily transition probabilities were applied for the AKI cohort, because of a limited number of data from the LTHT AKI registry on patients post cardiac surgery. Similarly, other key parameters in this analysis are not specific to this patient subgroup, for example early AKI treatment costs and impact, follow-up costs, mortality and utility and follow-up risk of CKD.
- We have been unable to externally validate the model (i.e. compare the estimated model outputs to real-world data) because of a paucity of data with which to externally validate against. As a result, although we have conducted extensive internal validation and cross-validation (comparing the model outputs with those of other economic evaluations), the model results should be interpreted with caution.

Cost-effectiveness analysis

Cost-effectiveness is measured in terms of the ICER and the INB.

The ICER is calculated by dividing the difference in mean costs between two arms by the difference in mean health effects (QALYs) between the two arms:

$$ICER = \frac{C_T - C_{SC}}{E_T - E_{SC}} = \frac{\Delta C}{\Delta E}, \quad (12)$$

where C_T and E_T are the expected cost and effectiveness of the intervention (i.e. test arm), C_{SC} and E_{SC} are the expected cost and effectiveness of the standard care arm and ΔC and ΔE are the incremental cost and effect, respectively, of the test arm compared with the standard care arm.

Assuming that the intervention is more costly and more effective than standard care, the ICER represents the additional cost required to be spent on the intervention to gain an additional unit of health. The cost-effectiveness of an intervention is determined by whether or not this ICER falls above or below the decision-maker's willingness-to-pay per additional QALY (i.e. 'threshold'). In the UK, NICE currently adopts

a threshold value of £20,000 per QALY; if a new intervention has an ICER of < £20,000 per additional QALY then it is likely to be considered a cost-effective use of NHS resources, whereas an ICER of > £20,000 indicates that the intervention is not expected to be a cost-effective use of resources or is required to meet additional criteria. This decision rule is expressed using the following formula:

$$\frac{\Delta C}{\Delta E} < \lambda, \tag{13}$$

where λ is the adopted willingness-to-pay threshold.

When the threshold is known, we can divide the incremental cost by the threshold value to convert this value onto the QALY scale (or, conversely, multiply the QALYs by the threshold to express QALYs on the monetary scale). For example, if the threshold is £20,000 and the intervention has an additional cost of £10,000, we can calculate that this cost is equivalent to 0.5 QALYs. This allows us to rearrange the ICER formula to express the overall INB on the QALY scale or the incremental net monetary benefit (INMB) on the monetary scale:

$$INB = \Delta E - \frac{\Delta C}{\lambda} \tag{14}$$

$$INMB = \Delta E * \lambda - \Delta C. \tag{15}$$

Unlike the ICER, for which the exact interpretation of cost-effectiveness depends on whether or not the incremental cost and QALYs are positive or negative, the interpretation of the INB is straightforward: for any given set of strategies, the strategy with the greatest INB (or INMB) is the most cost-effective alternative. In addition, the favourable mathematical properties of the INB allow for more straightforward computation of the cost-effectiveness probabilities and, therefore, the INBs are presented alongside the ICERs for each of the analyses.

Cost-effectiveness was assessed by comparing each testing strategy with standard care in turn. In addition, a full incremental analysis, including all of the available tests within one evaluation, was conducted. In this approach testing strategies are ranked in order of increasing cost and any options that are either dominated (i.e. produce fewer QALYs for a greater cost than the next best alternative) or extendedly dominated (i.e. produce fewer QALYs for a greater cost than a linear combination of two alternatives) are removed. ICERs for the remaining strategies (now ordered in terms of increasing cost and QALYs) are then recalculated by comparing each strategy in turn to the next best alternative (i.e. the next most costly and effective strategy).[479]

Sensitivity analysis

All model base-case analyses were run using probabilistic sensitivity analysis using 10,000 Monte Carlo simulations of the model. This accounts for joint parameter uncertainty in non-linear models by assigning probability distributions to each of the input parameters (using available variance data) and randomly drawing from these probabilities over the 10,000 simulations. The results are presented as a scatterplot on the cost-effectiveness plane (which presents incremental costs and QALYs for each intervention compared with standard care), with all base-case analyses assuming a willingness-to-pay threshold of £20,000. In addition, the results are presented using cost-effectiveness acceptability frontiers (CEAFs) to show (1) the probability that an intervention is cost-effective across different willingness-to-pay thresholds (range £0–150,000) and (2) which strategy is optimal based on having the highest mean net benefit (i.e. the 'frontier').

For each testing strategy a series of one-way sensitivity analyses was conducted, using 5000 simulations of the model. In the case of NGAL and cystatin C, for which multiple tests are available (i.e. plasma, urine and

serum), the one-way sensitivity analyses were run only for the test found to have the highest probability of being cost-effective in the primary CEA.

The following one-way sensitivity analyses were conducted:

1. *SA1: time horizon (base case: lifetime)*. A range of alternative time horizons were considered: 90 days (i.e. hospital period), 1 year (+90 days), 5 years (+90 days), 10 years (+90 days) and 20 years (+90 days).
2. *SA2: test costs (base-case fixed costs: Nephrocheck £71.27, NGAL £14.99, cystatin C £4.62)*. A range of low and high test costs were explored, equal to 0.25, 0.5, 1.5, 2 and 5 times the base-case values.
3. *SA3: AKI incidence (base case: mean 0.317, SD 0.018)*. A sensitivity analysis was conducted using a range of alternative values for the incidence of AKI in the ICU: 10%, 20%, 40% and 50%.
4. *SA4: impact of the early AKI Intervention RR parameter (base case: mean RR 0.78, SD 0.25)*. Two sensitivity analyses were conducted around this key parameter:

    i. Low-/high-impact scenarios – A sensitivity analysis was conducted assuming alternative values for the RR (0.2, 0.4, 0.6, 0.7, 0.9 and 0.95) to explore the possibility that early AKI intervention may be more or less effective than estimated in the base case.
    ii. Distribution adjustments – Ideally, a beta distribution would have been adopted for this parameter to ensure that the value was between 0 and 1 (i.e. that appropriate early intervention always resulted in improved outcomes). However, because of the high uncertainty around this parameter the beta distribution could not be used. In the base case this parameter was therefore drawn from a log-normal distribution, which maintains the expected 'bell' shape at the cost of allowing values > 1 (meaning that in some cases early AKI intervention leads to increased AKI risks). Two alternative parameterisations were explored: (1) truncating the distribution at 1 (i.e. recoding values > 1 to = 1) and (2) reducing the parameter uncertainty to allow beta estimation (SD 0.06).

5. *SA5: cost of early AKI intervention (base case: mean £205, SD £279)*. A sensitivity analysis was conducted assuming alternative costs for early AKI intervention (£50, £100, £500, £800).
6. *SA6: ICU utility (base case: mean –0.402, SD 0.201)*. A sensitivity analysis was conducted assuming alternative mean values of 0 and 0.2 for ICU utility, as there was a paucity of data for this value.
7. *SA7: test accuracy adjustment (FP cases reset to TPs and overall incidence of AKI increased)*. The diagnostic accuracy studies informing the base-case sensitivity and specificity estimates for each of the tests were conducted using standard care testing as the reference standard, assuming that standard care perfectly identifies patients with and without AKI. However, standard care tests are known to be imperfect and, in particular, are expected to currently fail to identify many patients with early renal injury. An exploratory sensitivity analysis was conducted for each testing strategy assuming that 10%, 25%, 50% or 100% of test FP results are actually TP results (i.e. cases of early AKI that standard care testing failed to identify), with the associated reduced risks of AKI progression as a result of early AKI intervention. For simplicity, in the testing arms all of these extra cases of AKI were assumed to have a KDIGO AKI stage of S1. This analysis results in the overall incidence of AKI increasing by the proportion of FP results that have been recoded to TP results and the incidence of AKI is increased in the baseline arm to reflect this change.
8. *SA8: negative impact of FP test results (increased mortality)*. The base-case analysis assumes no negative health consequences for patients falsely identified as having AKI. It is possible that these patients could suffer if, for example, access to required nephrotoxic agents, scans or other treatments is delayed. A sensitivity analysis was conducted assuming that, on average, patients with FP test results would experience a 5%, 10%, 30% or 50% increased risk of mortality while in the ICU.
9. *SA9: impact of negative test results (reduction in monitoring leading to cost saving plus mortality risk for FNs)*. The focus of the base-case analysis was on the impact of testing on patients correctly diagnosed early. Testing may also enable reduced intensity of treatment or monitoring for patients with negative test results, at the expense of potentially worse outcomes for patients with FN results (as above). A sensitivity analysis was conducted, assuming that all patients with negative test results with early AKI (KDIGO ≤ S1) would have a reduced cost of ICU care (–£100) and that patients with FN results with early AKI would incur an increased mortality risk of 10%.

Cost-effectiveness results

Nephrocheck compared with standard care

Base case (adult intensive care unit all-comers)

The results for the base-case CEA of Nephrocheck testing compared with standard care are presented in *Table 53*. The addition of Nephrocheck testing on admission to the ICU for an all-comer adult population is expected to have a lifetime additional cost of £301 and an additional health benefit of 0.016 QALYs per patient. This results in an ICER of £19,324 per additional QALY, with a mean positive INB of 0.001 QALYs (equivalent to £20 in terms of INMB).

The uncertainty around the model results can be seen in *Figure 35*. Although the mean ICER (£19,324) lies below the threshold line (indicating cost-effectiveness), the expected incremental cost and QALY results vary widely, with a significant proportion of points lying in non-cost-effective regions (i.e. above the threshold line).

The uncertainty around the test cost-effectiveness over alternative thresholds is presented in the CEAF in *Figure 36*. Above a threshold of £19,400 per QALY, Nephrocheck testing is expected to be the most cost-effective strategy. The test has a 48% probability of being cost-effective at a £20,000 per QALY threshold, increasing to 54% at a £50,000 per QALY threshold.

Secondary analysis (post-cardiac surgery subgroup)

The results of the secondary analysis are presented in *Table 54*. The addition of Nephrocheck testing in this setting is expected to have a lifetime additional cost of £205 and produce an additional 0.011 QALYs per patient. This results in an ICER of £18,617 per QALY, with a mean INB of 0.001 QALYs (equivalent to £20 in terms of INMB). At a £20,000 per QALY threshold there is a 50% probability that Nephrocheck testing is cost-effective in this subgroup, rising to 54% at a threshold of £50,000 (CEAF not shown).

Sensitivity analyses

The results of the one-way sensitivity analyses conducted for Nephrocheck testing compared with standard care are provided in *Table 55*. Nephrocheck testing is no longer cost-effective (i.e. has an ICER of $>$ £20,000 per QALY) when (1) the time horizon is reduced to $\leq$ 20 years (SA1), (2) the test cost is increased by $\geq$ 50% (i.e. to $\geq$ £106.91) (SA2), (3) the incidence of AKI in the ICU is reduced to $\leq$ 20% (from 31.7% in the base case) (SA3), (4) the impact of early AKI intervention is limited to a $\leq$ 10% reduction in AKI risks (from 22% in the base case) (SA4), (5) the cost of early AKI intervention is increased to £500 or £800 (£205 in the base case) (SA5), (6) FP test results are assumed to lead to a $\geq$ 5% increased risk of ICU mortality (SA8) and (7) negative test results are assumed to lead to a £100 cost saving (because of diminished monitoring) and a simultaneous 10% increased mortality rate for FPs (SA9). In contrast, the only instances when the probability that Nephrocheck testing is cost-effective rises above 60% are when 25%, 50% or 100% of FP test results are assumed to have actually been TP results (with the incidence of AKI increasing to 40%, 49% and 66% respectively). In these cases the ICER falls below £10,000 per QALY (SA7).

Neutrophil gelatinase-associated lipocalin compared with standard care

Base case (adult intensive care unit all-comers)

The results for the base-case CEA of NGAL testing compared with standard care are shown in *Table 56*. NGAL testing is associated with a lifetime additional cost of £164–215 (depending on the specific test) and an additional health benefit of 0.012–0.016 QALYs. This results in ICERs of £13,372–13,828 per additional QALY, with mean INBs of 0.004–0.005 (equivalent to £80–100 in terms of INMB). At a threshold value of £20,000 per additional QALY, NGAL (plasma) testing has the highest probability of being cost-effective (51.9%) and is therefore explored in the sensitivity analysis.

TABLE 53 Results of the primary CEA (ICU all-comer population): Nephrocheck vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	32,596 (24,320 to 43,145)	5.61 (0.46 to 9.09)				3.979 (–1.14 to 7.34)				
Nephrocheck	32,897 (24,662 to 43,484)	5.62 (0.46 to 9.12)	301 (–1087 to 1713)	0.016 (–0.16 to 0.20)	19,324	3.985 (–1.15 to 7.33)	0.001 (–0.12 to 0.13)	0.57	0.32	0.48

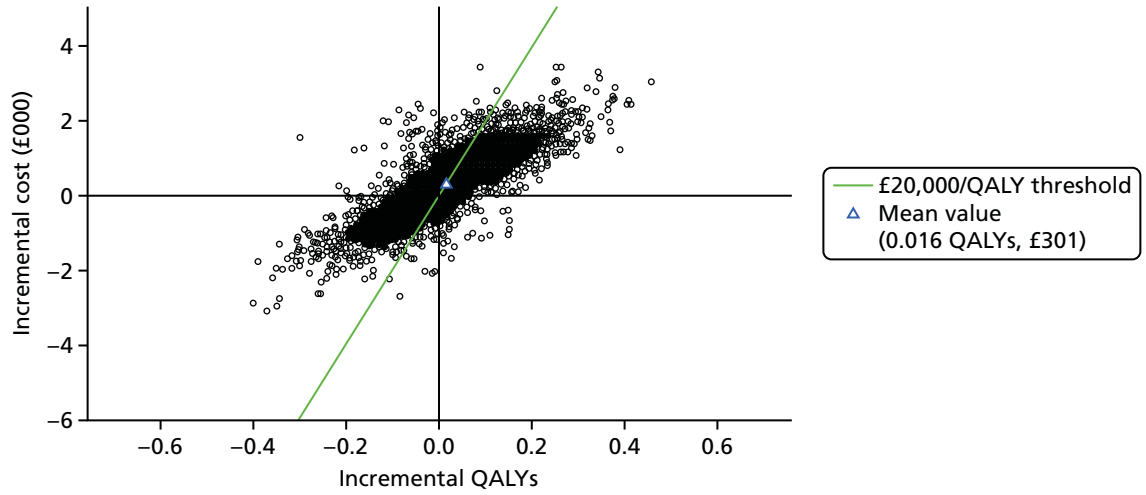

FIGURE 35 Scatterplot: incremental costs and QALYs for Nephrocheck vs. standard care (base case).

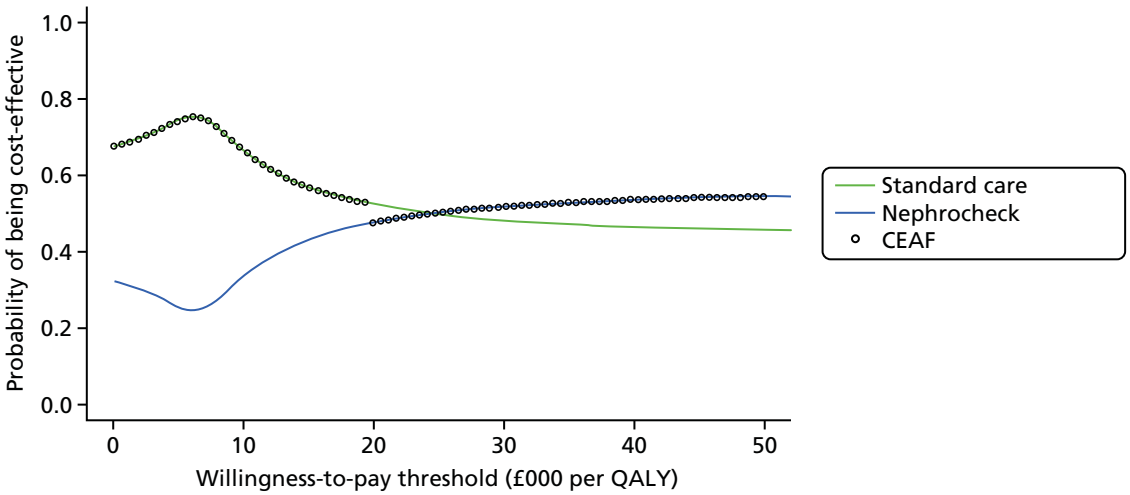

FIGURE 36 Cost-effectiveness acceptability frontier: Nephrocheck vs. standard care (base case).

The uncertainty around the results for NGAL (plasma) testing is shown in *Figures 37* and *38* [the results for NGAL (urine) and (serum) testing have a very similar distribution and are not presented]. As for Nephrocheck testing, although the mean ICER for NGAL (plasma) testing (£13,372) lies below the threshold line, the individual simulation points vary widely. Above a threshold of £13,400 per QALY, NGAL (plasma) testing is expected to be the most cost-effective strategy. The test has a 52% probability of being cost-effective at a £20,000 per QALY threshold, increasing to and levelling out at 56% at a £50,000 per QALY threshold.

Secondary analysis (post-cardiac surgery subgroup)

The results of the secondary analysis conducted in a subgroup of patients after cardiac surgery are presented in *Table 57*. In this subgroup, NGAL testing is expected to have a lifetime additional cost of £137–172 and produce an additional health benefit of 0.008–0.012 QALYs per patient. This results in ICERs ranging from £13,051 to £19,287 per additional QALY, with mean INBs of 0.001–0.004 QALYs.

TABLE 54 Results of the secondary CEA (post-cardiac surgery subgroup): Nephrocheck vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	29,959 (22,738 to 37,726)	6.50 (0.56 to 10.20)				5.01 (–0.90 to 8.60)				
Nephrocheck	30,163 (22,893 to 37,942)	6.52 (0.56 to 10.20)	205 (–850 to 1249)	0.011 (–0.13 to 0.15)	18,617	5.01 (–0.91 to 8.60)	0.001 (–0.09 to 0.10)	0.57	0.34	0.50

TABLE 55 Sensitivity analyses: Nephrocheck vs. standard care

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Base-case analysis (for comparison)										
Nephrocheck base case	32,897	5.62	301	0.016	19,323	3.99	0.001	0.57	0.32	0.48
SA1: time horizon (base case: lifetime, i.e. approximately 40 years)										
90 days	13,928	0.05	210	0.000	1,679,292	–0.64	–0.010	0.54	0.26	0.25
1 year (+90 days)	17,626	0.52	232	0.002	150,509	–0.36	–0.010	0.57	0.26	0.23
5 years (+90 days)	25,732	2.02	264	0.006	43,783	0.73	–0.007	0.57	0.29	0.30
10 years (+90 days)	29,626	3.38	283	0.010	27,816	1.90	–0.004	0.58	0.31	0.41
20 years (+90 days)	31,859	5.04	302	0.015	20,163	3.45	0.000	0.57	0.32	0.47
SA2: Nephrocheck test cost (base-case cost £71.27)										
Test cost × 0.25 = £17.82	32,901	5.62	263	0.017	15,648	3.98	0.004	0.57	0.35	0.50
Test cost × 0.50 = £35.64	32,918	5.62	279	0.017	16,640	3.98	0.003	0.57	0.34	0.49
Test cost × 1.50 = £106.91	32,985	5.62	346	0.017	20,608	3.97	–0.001	0.57	0.30	0.46
Test cost × 2.0 = £142.54	33,018	5.62	379	0.017	22,591	3.97	–0.002	0.57	0.29	0.45
Test cost × 5.0 = £365.35	33,226	5.62	588	0.017	34,995	3.96	–0.013	0.57	0.19	0.36
SA3: ICU AKI incidence (base case: mean 0.317, SD 0.018)										
AKI incidence = 0.10	32,558	6.26	237	0.005	45,241	4.63	–0.007	0.59	0.16	0.33
AKI incidence = 0.20	32,768	5.97	273	0.010	26,096	4.33	–0.003	0.59	0.26	0.44
AKI incidence = 0.40	33,187	5.39	346	0.021	16,523	3.73	0.004	0.59	0.33	0.50
AKI incidence = 0.50	33,397	5.10	383	0.026	14,609	3.43	0.007	0.59	0.35	0.52

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
SA4: impact of early AKI intervention on AKI risks (base case: RR 0.78, SD 0.25)										
RR = 0.20 (i.e. 80% reduced risks)	33,171	5.66	532	0.051	10,347	3.997	0.025	0.68	0.26	0.59
RR = 0.40 (60% reduced risks)	33,125	5.65	487	0.044	11,026	3.992	0.020	0.68	0.26	0.59
RR = 0.60 (40% reduced risks)	33,052	5.64	413	0.033	12,702	3.984	0.012	0.65	0.28	0.55
RR = 0.70 (30% reduced risks)	33,006	5.63	367	0.025	14,471	3.980	0.007	0.63	0.29	0.52
RR = 0.90 (10% reduced risks)	32,898	5.61	260	0.009	29,199	3.969	–0.004	0.55	0.34	0.43
RR = 0.95 (5% reduced risks)	32,868	5.61	230	0.004	52,500	3.965	–0.007	0.52	0.35	0.41
RR values > 1 reset to 1	32,973	5.62	335	0.020	16,406	3.976	0.004	0.59	0.31	0.49
RR SD reduced to 0.06	32,963	5.62	325	0.019	17,249	3.975	0.003	0.60	0.30	0.49
SA5: cost of early AKI intervention (base case: mean cost £205, SD £279)										
Cost of early AKI treatment = £50	32,843	5.62	205	0.017	12,180	3.979	0.007	0.57	0.38	0.53
Cost of early AKI treatment = £100	32,871	5.62	232	0.017	13,824	3.978	0.005	0.57	0.37	0.51
Cost of early AKI treatment = £500	33,092	5.62	453	0.017	26,975	3.967	–0.006	0.57	0.24	0.41
Cost of early AKI treatment = £800	33,257	5.62	619	0.017	36,839	3.958	–0.014	0.57	0.17	0.34
SA6: ICU utility (base case: mean –0.402, SD 0.201)										
ICU utility = 0.00	32,947	5.63	309	0.017	18,704	3.982	0.001	0.57	0.33	0.47
ICU utility = 0.20	32,947	5.63	309	0.017	18,690	3.987	0.001	0.57	0.33	0.47

continued

TABLE 55 Sensitivity analyses: Nephrocheck vs. standard care (*continued*)

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
SA7: test accuracy adjustment (FPs reset to TPs and overall incidence of AKI increased)										
10% of FP results recoded as TPs (AKI S1) and overall incidence of AKI increased to 35.2%	33,161	5.54	418	0.035	11,857	3.882	0.014	0.65	0.28	0.56
25% of FP results recoded as TPs (AKI S1) and overall incidence of AKI increased to 40.4%	33,326	5.41	559	0.061	9228	3.740	0.033	0.72	0.24	0.66
50% of FP results recoded as TPs (AKI S1) and overall incidence of AKI increased to 49%	33,751	5.20	774	0.102	7620	3.508	0.063	0.80	0.21	0.76
100% of FP results recoded as TPs (AKI S1) and overall incidence of AKI increased to 66.4%	34,489	4.76	1217	0.184	6606	3.039	0.123	0.87	0.18	0.84
SA8: increased mortality for FP results										
5% increased ICU mortality for FPs	32,877	5.61	£238	0.004	63,268	3.964	–0.008	0.50	0.36	0.41
10% increased ICU mortality for FPs	32,803	5.60	£165	–0.009	Dominated	3.955	–0.017	0.44	0.41	0.34
30% increased ICU mortality for FPs	32,517	5.54	–121	–0.060	2035[a]	3.919	–0.053	0.25	0.57	0.18
50% increased ICU mortality for FPs	32,244	5.50	–394	–0.108	3646[a]	3.884	–0.088	0.15	0.69	0.11
SA9: impact of negative test results (reduction in monitoring leading to cost saving + increased mortality risk for FNs)										
One-off cost saving (–£100) + 10% increased ICU mortality for FNs	32,558	5.58	–80	–0.020	4100[a]	3.957	–0.016	0.40	0.55	0.38

a Cost saved per QALY lost: in these cases the ICER must be > £20,000 (i.e. > £20,000 saved per QALY lost) to be considered cost-effective. In these instances Nephrocheck testing is therefore not cost-effective.

TABLE 56 Results of the primary CEA (ICU all-comer population): NGAL vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	32,596 (24,320 to 43,145)	5.61 (0.46 to 9.09)				3.979 (–1.14 to 7.34)				
NGAL (urine)	32,759 (24,521 to 43,351)	5.62 (0.46 to 9.11)	164 (–1179 to 1517)	0.0119 (–0.16 to 0.19)	13,742	3.985 (–1.15 to 7.33)	0.004 (–0.11 to 0.13)	0.56	0.40	0.514
NGAL (plasma)	32,759 (24,516 to 43,339)	5.62 (0.46 to 9.11)	164 (–1180 to 1510)	0.0122 (–0.16 to 0.19)	13,372	3.983 (–1.15 to 7.33)	0.004 (–0.11 to 0.13)	0.56	0.40	0.519
NGAL (serum)	32,811 (24,587 to 43,427)	5.62 (0.46 to 9.11)	215 (–1167 to 1619)	0.0156 (–0.16 to 0.20)	13,828	3.987 (–1.15 to 7.33)	0.005 (–0.11 to 0.14)	0.57	0.37	0.517

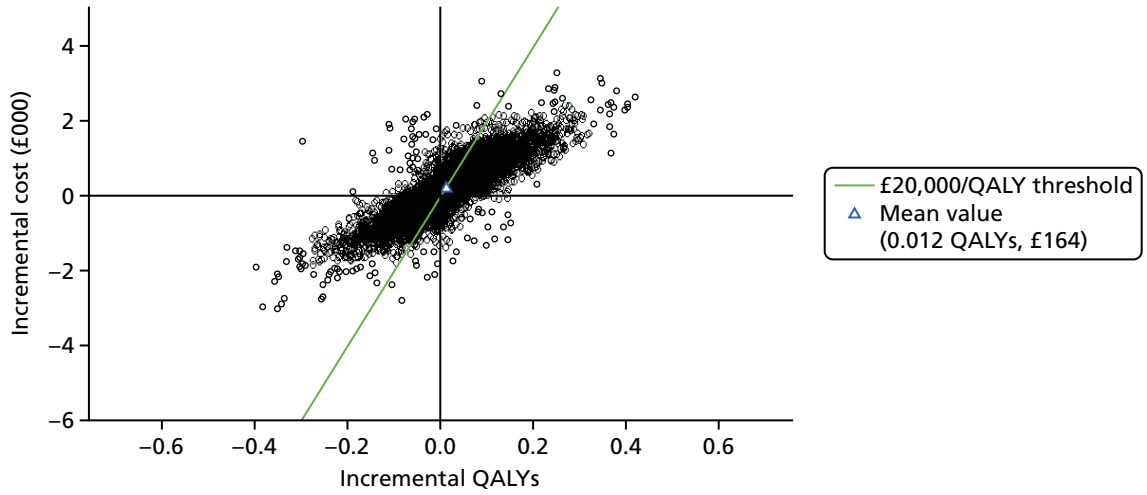

FIGURE 37 Scatterplot: incremental costs and QALYs for NGAL (plasma) vs. standard care (base case).

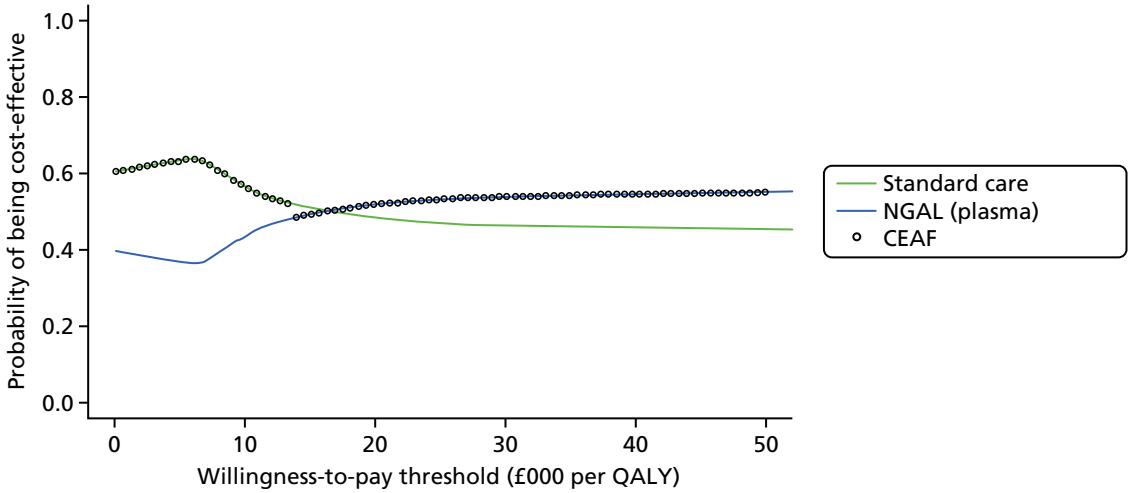

FIGURE 38 Cost-effectiveness acceptability frontier: NGAL (plasma) vs. standard care (base case).

Sensitivity analyses

The results of the one-way sensitivity analyses conducted for NGAL (plasma) testing compared with standard care are provided in *Table 58*. NGAL testing is no longer cost-effective (i.e. has an ICER of > £20,000 per QALY) when (1) the time horizon is ≤ 5 years (SA1), (2) the incidence of AKI in the ICU is reduced to 10%, (from 31.7% in the base case) (SA3), (3) the impact of early AKI intervention is limited to a 5% reduction in AKI risks (from 22%) (SA4), (4) the cost of early AKI intervention is increased to £800 (from £205) (SA5), (5) FP test results result in a ≥ 10% increase in ICU mortality for those patients (SA8) and (6) negative test results are assumed to lead to a £100 cost saving (because of diminished monitoring) and a 10% increased mortality rate for FPs. In contrast, the only instances when the probability that NGAL testing is cost-effective rises above 60% are when the impact of early AKI intervention is increased to a ≥ 60% reduction in AKI risks (SA4) and when 25%, 50% or 100% of FP test results are assumed to have actually been TP test results (with corresponding increases in AKI incidence of 35%, 38% and 45%) (SA7).

Cystatin C compared with standard care

Base case (adult intensive care unit all-comers)

The results for the base-case CEA of cystatin C testing compared with standard care are shown in *Table 59*. Cystatin C testing is expected to have a lifetime additional cost of £149–166 (depending on the specific

TABLE 57 Results of the secondary CEA (post-cardiac surgery subgroup): NGAL vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	29,959 (22,738 to 37,726)	6.50 (0.56 to 10.20)				5.007 (–0.90 to 8.60)				
NGAL (plasma)	30,096 (22,836 to 37,867)	6.51 (0.56 to 10.21)	137 (–895 to 1178)	0.008 (–0.13 to 0.14)	16,709	5.008 (–0.90 to 8.60)	0.001 (–0.09 to 0.09)	0.56	0.39	0.50
NGAL (urine)	30,131 (22,885 to 37,900)	6.51 (0.56 to 10.21)	172 (–875 to 1225)	0.009 (–0.13 to 0.14)	19,287	5.007 (–0.90 to 8.60)	0.003 (–0.09 to 0.09)	0.56	0.36	0.48
NGAL (serum)	30,108 (22,845 to 37,892)	6.52 (0.56 to 10.22)	149 (–905 to 1204)	0.012 (–0.13 to 0.15)	13,051	5.011 (–0.90 to 8.60)	0.004 (–0.09 to 0.10)	0.57	0.38	0.52

TABLE 58 One-way sensitivity analyses: NGAL (plasma) vs. standard care

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Base-case analysis (for comparison)										
NGAL (plasma) base case	32,759	5.62	164	0.0122	13,372	3.983	0.004	0.56	0.40	0.52
SA1: time horizon (base case: lifetime, i.e. approximately 40 years)										
90 days	13,808	0.05	90	0.000	978,005	–0.64	–0.004	0.53	0.38	0.37
1 year (+90 days)	17,504	0.52	110	0.001	89,683	–0.35	–0.004	0.56	0.37	0.35
5 years (+90 days)	25,603	2.02	135	0.005	28,191	0.74	–0.002	0.56	0.38	0.42
10 years (+90 days)	29,493	3.38	150	0.008	18,517	1.90	0.001	0.56	0.39	0.49
20 years (+90 days)	31,723	5.04	165	0.012	13,819	3.45	0.004	0.56	0.39	0.52
SA2: NGAL test cost (base-case cost £14.98)										
Test cost × 0.25 = £3.745	32,802	5.62	163	0.013	12,180	3.98	0.005	0.56	0.40	0.52
Test cost × 0.50 = £7.49	32,805	5.62	167	0.013	12,442	3.98	0.005	0.56	0.40	0.52
Test cost × 1.50 = £22.47	32,819	5.62	181	0.013	13,487	3.98	0.004	0.56	0.39	0.52
Test cost × 2.0 = £29.96	32,826	5.62	188	0.013	14,010	3.98	0.004	0.56	0.38	0.51
Test cost × 5.0 = £74.90	32,868	5.62	230	0.013	17,145	3.97	0.002	0.56	0.36	0.49
SA3: ICU AKI incidence (base case: mean 0.317, SD 0.018)										
AKI incidence = 0.10	32,420	6.26	98	0.004	23,909	4.63	–0.001	0.58	0.31	0.46
AKI incidence = 0.20	32,628	5.96	133	0.008	16,211	4.33	0.002	0.58	0.36	0.51
AKI incidence = 0.40	33,045	5.38	204	0.016	12,363	3.73	0.006	0.58	0.39	0.53
AKI incidence = 0.50	33,253	5.09	239	0.021	11,593	3.43	0.009	0.58	0.40	0.54

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
SA4: impact of early AKI intervention on AKI risks (base case: RR 0.78, SD 0.25)										
RR = 0.20 (i.e. 80% reduced risks)	32,988	5.65	349	0.041	8497	3.996	0.024	0.66	0.33	0.61
RR = 0.40 (60% reduced risks)	32,951	5.64	313	0.035	8871	3.992	0.020	0.66	0.33	0.61
RR = 0.60 (40% reduced risks)	32,892	5.63	254	0.026	9780	3.986	0.013	0.62	0.35	0.58
RR = 0.70 (30% reduced risks)	32,856	5.62	217	0.020	10,729	3.982	0.009	0.60	0.36	0.56
RR = 0.90 (10% reduced risks)	32,770	5.61	131	0.007	18,587	3.973	0.000	0.54	0.41	0.49
RR = 0.95 (5% reduced risks)	32,746	5.61	107	0.003	31,140	3.971	–0.002	0.52	0.43	0.46
RR values > 1 reset to 1	32,830	5.62	191	0.016	11,762	3.979	0.007	0.58	0.38	0.53
RR SD reduced to 0.06	32,822	5.62	183	0.015	12,208	3.978	0.006	0.58	0.38	0.53
SA5: cost of early AKI intervention (base case: mean cost £205, SD £279)										
Cost of early AKI treatment = £50	32,755	5.62	116	0.013	8669	3.980	0.008	0.56	0.43	0.55
Cost of early AKI treatment = £100	32,769	5.62	131	0.013	9763	3.979	0.007	0.56	0.42	0.54
Cost of early AKI treatment = £500	32,887	5.62	248	0.013	18,519	3.974	0.001	0.56	0.35	0.48
Cost of early AKI treatment = £800	32,975	5.62	336	0.013	25,085	3.969	–0.003	0.56	0.30	0.43
SA6: ICU utility (base case: mean –0.402, SD 0.201)										
ICU utility = 0.00	32,809	5.63	170	0.013	12,983	3.986	0.005	0.56	0.40	0.52
ICU utility = 0.20	32,810	5.63	171	0.014	12,654	3.991	0.005	0.56	0.39	0.52
SA7: test accuracy adjustment (FPs reset to TPs and overall incidence of AKI increased)										
10% of FP results recoded as TPs (AKI S1) and overall incidence of AKI increased to 33.0%	32,926	5.59	221	0.021	10,335	3.945	0.010	0.61	0.37	0.56
25% of FP results recoded as TPs and overall incidence of AKI increased to 34.9%	32,952	5.54	280	0.031	8932	3.890	0.017	0.64	0.34	0.60

continued

TABLE 58 One-way sensitivity analyses: NGAL (plasma) vs. standard care (*continued*)

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
50% of FP results recoded as TPs and overall incidence of AKI increased to 38.2%	33,149	5.46	354	0.046	7678	3.804	0.028	0.69	0.32	0.66
100% of FP results recoded as TPs and overall incidence of AKI increased to 44.7%	33,423	5.30	521	0.077	6752	3.629	0.051	0.77	0.27	0.75
SA8: increased mortality for FP results										
5% increased ICU mortality for FPs	32,784	5.61	146	0.009	17,108	3.974	0.001	0.53	0.41	0.49
10% increased ICU mortality for FPs	32,757	5.61	118	0.004	32,218	3.970	–0.002	0.51	0.43	0.46
30% increased ICU mortality for FPs	32,647	5.59	8	–0.016	Dominated	3.957	–0.016	0.41	0.50	0.36
50% increased ICU mortality for FPs	32,539	5.57	–100	–0.035	2884[a]	3.943	–0.030	0.32	0.56	0.27
SA9: impact of negative test results (reduction in monitoring leading to cost saving + increased mortality risk for FNs)										
One-off cost saving (–£100) + 10% increased ICU mortality for FNs	31,753	5.52	–885	–0.088	10,064[a]	3.929	–0.044	0.15	0.91	0.25

a Cost saved per QALY lost: in these cases the ICER must be > £20,000 (i.e. > £20,000 saved per QALY lost) to be considered cost-effective. In these instances Nephrocheck testing is therefore not cost-effective.

TABLE 59 Results of the primary CEA (ICU all-comer population): cystatin C vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	32,596 (24,320 to 43,145)	5.61 (0.46 to 9.09)				3.979 (–1.14 to 7.34)				
Cystatin C (urine)	32,751 (24,524 to 43,347)	5.62 (0.46 to 9.11)	155 (–1187 to 1500)	0.0115 (–0.16 to 0.19)	13,449	3.985 (–1.15 to 7.33)	0.004 (–0.11 to 0.13)	0.56	0.40	0.52
Cystatin C (plasma)	32,761 (24,546 to 43,355)	5.62 (0.46 to 9.11)	166 (–1183 to 1524)	0.0123 (–0.16 to 0.20)	13,504	3.983 (–1.15 to 7.32)	0.004 (–0.11 to 0.13)	0.56	0.40	0.52
Cystatin C (serum)	32,744 (24,320 to 43,340)	5.62 (0.46 to 9.11)	149 (–1201 to 1496)	0.0130 (–0.16 to 0.19)	11,476	3.986 (–1.15 to 7.33)	0.006 (–0.11 to 0.13)	0.56	0.42	0.54

test) and produce an additional 0.012–0.013 QALYs. This results in ICERs ranging from £11,476 to £13,504 per additional QALY, with INBs of 0.004–0.006 QALYs (equivalent to £80–120 in terms of INMB). At a threshold of £20,000 per QALY, cystatin C (serum) testing has the highest probability of being cost-effective (54%) and was explored in the sensitivity analysis.

The uncertainty around the cost-effectiveness of cystatin C (serum) testing is illustrated in *Figures 39* and *40* [the results for cystatin C (urine) and cystatin C (plasma) testing have a very similar distribution and are not presented]. Above a threshold of £11,500 per QALY, cystatin C (serum) testing is expected to be the most cost-effective strategy. The test has a 54% probability of being cost-effective at a £20,000 per QALY threshold, increasing to and levelling out at 56% at a £50,000 per QALY threshold.

Secondary analysis (post-cardiac surgery subgroup)

The results of the secondary analysis conducted within a subgroup of patients after cardiac surgery in the ICU are presented in *Table 60*. In this subgroup, the addition of cystatin C testing is expected to have a lifetime additional cost of £124–166 and produce an additional health benefit of 0.007–0.01 QALYs per patient. This results in ICERs ranging from £15,337 to £20,435 per additional QALY, with mean INBs of –0.0002 to +0.002 QALYs.

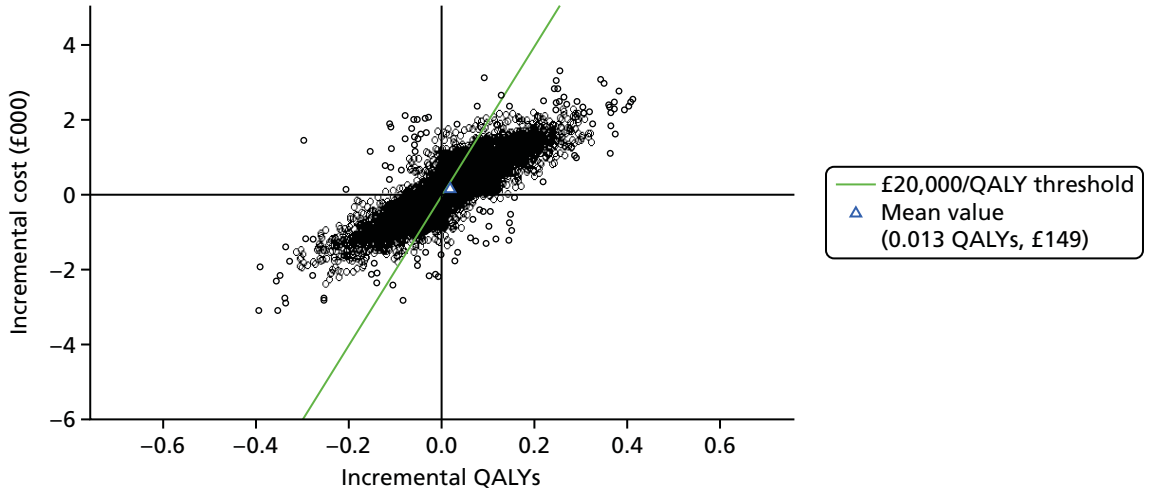

FIGURE 39 Scatterplot: incremental costs and QALYs for cystatin C (serum) vs. standard care (base case).

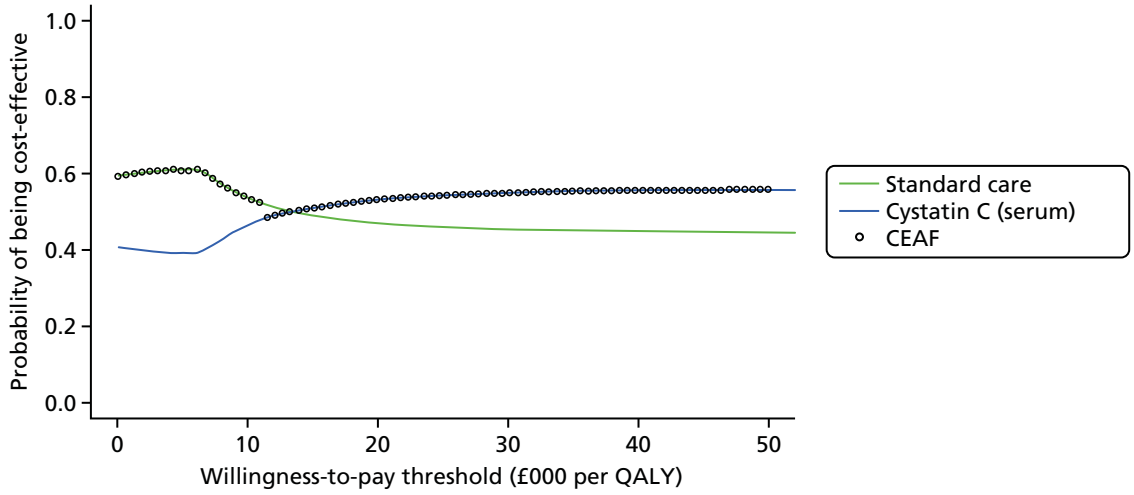

FIGURE 40 Cost-effectiveness acceptability frontier: cystatin C (serum) vs. standard care (base case).

TABLE 60 Results of the secondary CEA (post-cardiac surgery subgroup): cystatin C vs. standard care

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Net benefit (QALYs) (95% CI)	INB (95% CI)	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Standard care	29,959 (22,738 to 37,726)	6.50 (0.56 to 10.19)				5.007 (–0.90 to 8.60)				
Cystatin C (plasma)	32,125 (22,879 to 37,889)	6.51 (0.56 to 10.21)	166 (–881 to 1229)	0.008 (–0.13 to 0.14)	20,435	5.007 (–0.90 to 8.60)	–0.0002 (–0.09 to 0.09)	0.56	0.37	0.48
Cystatin C (urine)	30,082 (22,816 to 37,856)	6.51 (0.56 to 10.21)	124 (–908 to 1162)	0.007 (–0.13 to 0.14)	18,076	5.008 (–0.90 to 8.59)	0.0007 (–0.09 to 0.09)	0.55	0.40	0.49
Cystatin C (serum)	30,111 (22,847 to 37,869)	6.51 (0.56 to 10.21)	153 (–900 to 1204)	0.010 (–0.13 to 0.15)	15,337	5.009 (–0.90 to 8.60)	0.0023 (–0.09 to 0.10)	0.57	0.38	0.51

Sensitivity analyses

The results of the one-way sensitivity analyses conducted for cystatin C (serum) testing compared with standard care are provided in *Table 61*. Based on the mean expected cost and QALY results, cystatin C is no longer cost-effective (i.e. has an ICER of > £20,000 per QALY) when (1) the time horizon is ≤ 5 years (SA1), (2) the impact of early AKI intervention is limited to a 5% reduction in AKI risks (from 22% in the base case) (SA4), (3) the cost of early AKI intervention is increased to £800 (from £205) (SA5), (4) patients with a FP test result have a ≥ 30% increased ICU mortality rate (SA8) and (5) negative test results are assumed to lead to a £100 cost saving (because of diminished monitoring) and a 10% increased mortality rate for FPs (SA9). In contrast, the only instances in which the probability that cystatin C is cost-effective rises above 60% are when the impact of early AKI intervention is increased to a ≥ 40% reduction in AKI risks (SA4) and when ≥ 50% of FP test results are assumed to have actually been TP test results (SA7).

Multiway incremental analysis

Base case (adult intensive care unit all-comers)

The results of the multiway incremental analysis for the base case are presented in *Table 62* (the ICER for each strategy compared with standard care is shown in the last column for reference). After ranking all strategies in order of increasing costs, cystatin C (urine), cystatin C (plasma), NGAL (urine) and NGAL (plasma) were found to be dominated by cystatin C (serum), producing fewer QALYs for a greater cost. After removal of all dominated options, cystatin C (serum), NGAL (serum) and Nephrocheck remained, with ICERs of £11,476, £25,492 and £12,855,101 per additional QALY respectively. Based on this analysis, NGAL (serum) and Nephrocheck are no longer expected to be cost-effective, assuming a willingness-to-pay threshold of £20,000 per additional QALY.

The CEAF including all available strategies is shown in *Figure 41a*. Above a threshold value of £11,400, cystatin C (serum) testing is expected to be the most cost-effective strategy (based on the expected mean net benefit values, indicated by the cost-effectiveness frontier), with a probability of cost-effectiveness of 27%, falling to 23% at a £20,000 per QALY threshold. Above a threshold of £25,400, NGAL (serum) testing is expected to be the most cost-effective strategy, with a probability of cost-effectiveness of 20%, rising to 26% at a £50,000 per QALY threshold.

Secondary analysis (post-cardiac surgery subgroup)

The results of the multiway incremental analysis for the secondary analysis (post-cardiac surgery subgroup) are presented in *Table 63* (the ICER for each strategy compared with standard care is shown in the last column for reference). After ranking all strategies in order of increasing costs, NGAL (serum) testing was found to dominate all other alternative strategies. Cystatin C (urine) and NGAL (plasma) testing are both extendedly dominated by NGAL (serum) testing, having higher ICERs, whereas the remaining tests are all strongly dominated, producing fewer QALYs at a greater cost than NGAL (serum) testing.

The CEAF including all available strategies is shown in *Figure 41b*. Above a threshold value of £13,100, NGAL serum is expected to be the most cost-effective strategy (based on the expected mean net benefit values, indicated by the cost-effectiveness frontier), with a probability of cost-effectiveness of 31%, rising to 34% at a £20,000 per QALY threshold.

Summary

An economic evaluation was conducted to assess the cost-effectiveness of biomarkers compared with standard care for the early identification of AKI in the ICU. Three tests were assessed: Nephrocheck, cystatin C and NGAL. Cystatin C and NGAL tests are currently available across three alternative media (plasma, urine and serum); each of these was considered as a separate test in the analysis, resulting in a total of seven testing strategies together with Nephrocheck. The evaluation consisted of an economic decision model, in which cost-effectiveness was assessed over a lifetime horizon from a UK NHS and PSS

TABLE 61 One-way sensitivity analyses: cystatin C (serum) vs. standard care

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
Base-case analysis (for comparison)										
Cystatin C (serum) base case	32,744	5.62	149	0.013	11,476	3.986	0.006	0.56	0.42	0.54
SA1: time horizon (base case: lifetime, i.e. approximately 40 years)										
90 days	13,789	0.05	71	0.000	713,786	–0.63	–0.003	0.53	0.40	0.40
1 year (+90 days)	17,486	0.52	92	0.001	71,008	–0.35	–0.003	0.57	0.39	0.38
5 years (+90 days)	25,587	2.02	118	0.005	23,397	0.74	–0.001	0.57	0.40	0.45
10 years (+90 days)	29,477	3.38	134	0.009	15,710	1.90	0.002	0.57	0.40	0.51
20 years (+90 days)	31,708	5.04	150	0.013	11,926	3.45	0.005	0.56	0.40	0.53
SA2: cystatin C test cost (base case cost £4.26)										
Test cost × 0.25 = £1.065	32,795	5.62	157	0.014	11,070	3.98	0.006	0.56	0.40	0.53
Test cost × 0.50 = £2.13	32,796	5.62	158	0.014	11,140	3.98	0.006	0.56	0.40	0.53
Test cost × 1.50 = £6.39	32,800	5.62	162	0.014	11,422	3.98	0.006	0.56	0.40	0.53
Test cost × 2.0 = £8.52	32,802	5.62	163	0.014	11,563	3.98	0.006	0.56	0.40	0.53
Test cost × 5.0 = £21.30	32,814	5.62	175	0.014	12,408	3.98	0.005	0.56	0.39	0.52
SA3: ICU AKI incidence (base case: mean 0.317, SD 0.018)										
AKI incidence = 0.10	32,395	6.26	74	0.00	17,035	4.64	0.001	0.58	0.35	0.50
AKI incidence = 0.20	32,608	5.96	114	0.009	13,048	4.33	0.003	0.58	0.38	0.53
AKI incidence = 0.40	33,033	5.38	192	0.017	11,055	3.73	0.008	0.58	0.40	0.54
AKI incidence = 0.50	33,246	5.09	232	0.022	10,656	3.43	0.010	0.58	0.40	0.55

continued

TABLE 61 One-way sensitivity analyses: cystatin C (serum) vs. standard care (*continued*)

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
SA4: impact of early AKI intervention on AKI risks (base case: RR 0.78, SD 0.25)										
RR = 0.20 (i.e. 80% reduced risks)	32,984	5.65	345	0.043	7958	3.999	0.026	0.67	0.33	0.62
RR = 0.40 (60% reduced risks)	32,945	5.64	307	0.037	8237	3.994	0.022	0.66	0.34	0.62
RR = 0.60 (40% reduced risks)	32,883	5.63	244	0.027	8911	3.988	0.015	0.63	0.35	0.60
RR = 0.70 (30% reduced risks)	32,844	5.63	205	0.021	9610	3.984	0.011	0.61	0.37	0.57
RR = 0.90 (10% reduced risks)	32,753	5.61	115	0.007	15,339	3.974	0.002	0.54	0.42	0.50
RR = 0.95 (5% reduced risks)	32,728	5.61	89	0.004	24,435	3.972	–0.001	0.52	0.44	0.48
RR values > 1 reset to 1	32,816	5.62	178	0.017	10,346	3.981	0.008	0.58	0.39	0.54
RR SD reduced to 0.06	32,808	5.62	170	0.016	10,699	3.980	0.007	0.58	0.39	0.55
SA5: cost of early AKI intervention (base case: mean cost £205, SD £279)										
Cost of early AKI treatment = £50	32,748	5.62	109	0.014	7740	3.981	0.009	0.56	0.43	0.56
Cost of early AKI treatment = £100	32,761	5.62	122	0.014	8643	3.981	0.008	0.56	0.42	0.55
Cost of early AKI treatment = £500	32,863	5.62	224	0.014	15,860	3.976	0.003	0.56	0.36	0.50
Cost of early AKI treatment = £800	32,939	5.62	301	0.014	21,273	3.972	–0.001	0.56	0.32	0.46
SA6: ICU utility (base case: mean –0.402, SD 0.201)										
ICU utility = 0.00	32,795	5.63	157	0.014	11,202	3.987	0.006	0.56	0.40	0.53
ICU utility = 0.20	32,795	5.63	157	0.014	11,194	3.992	0.006	0.56	0.40	0.53

Sensitivity analysis	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£)	Net benefit (QALYs)	INB	*P*(more effective)	*P*(cost saving)	*P*(cost-effective)
SA7: test accuracy adjustment (FPs reset to TPs and overall incidence of AKI increased)										
10% of FP results recoded as TPs and overall incidence of AKI increased to 32.5%	32,893	5.60	194	0.020	9770	3.958	0.010	0.60	0.38	0.56
25% of FP results recoded as TPs and overall incidence of AKI increased to 33.8%	32,887	5.57	236	0.026	8897	3.924	0.015	0.62	0.36	0.59
50% of FP results recoded as TPs and overall incidence of AKI increased to 35.8%	33,029	5.52	278	0.035	7831	3.870	0.022	0.66	0.35	0.63
100% of FP results recoded as TPs and overall incidence of AKI increased to 39.9%	33,206	5.42	382	0.055	6945	3.760	0.036	0.72	0.31	0.70
SA8: increased mortality for FP results										
5% increased ICU mortality for FPs	32,780	5.62	142	0.011	12,822	3.977	0.004	0.55	0.41	0.51
10% increased ICU mortality for FPs	32,763	5.61	124	0.008	15,539	3.974	0.002	0.53	0.42	0.50
30% increased ICU mortality for FPs	32,693	5.60	55	–0.004	Dominated	3.966	–0.007	0.46	0.47	0.43
50% increased ICU mortality for FPs	32,624	5.59	–14	–0.016	886[a]	3.957	–0.016	0.41	0.52	0.37
SA9: impact of negative test results (reduction in monitoring leading to cost saving + increased mortality risk for FNs)										
One-off cost saving (–£100) + 10% increased ICU mortality for FNs	31,881	5.53	–758	–0.072	10,471[a]	3.938	–0.034	0.21	0.85	0.31

a Cost saved per QALY lost: in these cases the ICER must be > £20,000 (i.e. > £20,000 saved per QALY lost) to be considered cost-effective. In these instances Nephrocheck testing is therefore not cost-effective.

TABLE 62 Multiway incremental cost-effectiveness results (primary analysis)

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Comparator[a]	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Exclusion reason	ICER vs. standard care (£)
Standard care	32,596 (24,320 to 43,145)	5.6092 (0.46 to 9.09)	–	–	–	–	–	–
Cystatin C (serum)	32,744 (24,320 to 43,340)	5.6221 (0.46 to 9.11)	Standard care	149 (–1201 to 1496)	0.013 (–0.16 to 0.19)	11,476	–	11,476
Cystatin C (urine)	32,751 (24,524 to 43,347)	5.6207 (0.46 to 9.11)	Cystatin C (serum)	6 (–111 to 114)	–0.0014 (–0.01 to 0.01)	–4405	Dominated by cystatin C (serum)	13,449
NGAL (urine)	32,759 (24,521 to 43,351)	5.6211 (0.46 to 9.11)	Cystatin C (serum)	15 (–65 to 84)	–0.0011 (–0.01 to 0.01)	–13,927		13,742
NGAL (plasma)	32,759 (24,516 to 43,339)	5.6214 (0.46 to 9.11)	Cystatin C (serum)	15 (–55 to 80)	–0.0007 (–0.01 to 0.01)	–20,733		13,372
Cystatin C (plasma)	32,761 (24,546 to 43,355)	5.6214 (0.46 to 9.11)	Cystatin C (serum)	17 (–59 to 106)	–0.0007 (–0.01 to 0.02)	–23,801		13,504
NGAL (serum)	32,811 (24,587 to 43,427)	5.6247 (0.46 to 9.11)	Cystatin C (serum)	67 (–39 to 257)	0.0026 (–0.01 to 0.02)	25,492	–	13,828
Nephrocheck	32,897 (24,662 to 43,484)	5.6248 (0.46 to 9.12)	NGAL (serum)	86 (9 to 227)	0.000007 (–0.01 to 0.01)	12,855,101	–	19,324

a In the multiway incremental analysis, for each test, after ranking strategies in order of increasing costs, the incremental cost and QALYs are calculated based on a comparison with the next best strategy, excluding any dominated or extendedly dominated options (i.e. excluding the shaded rows).

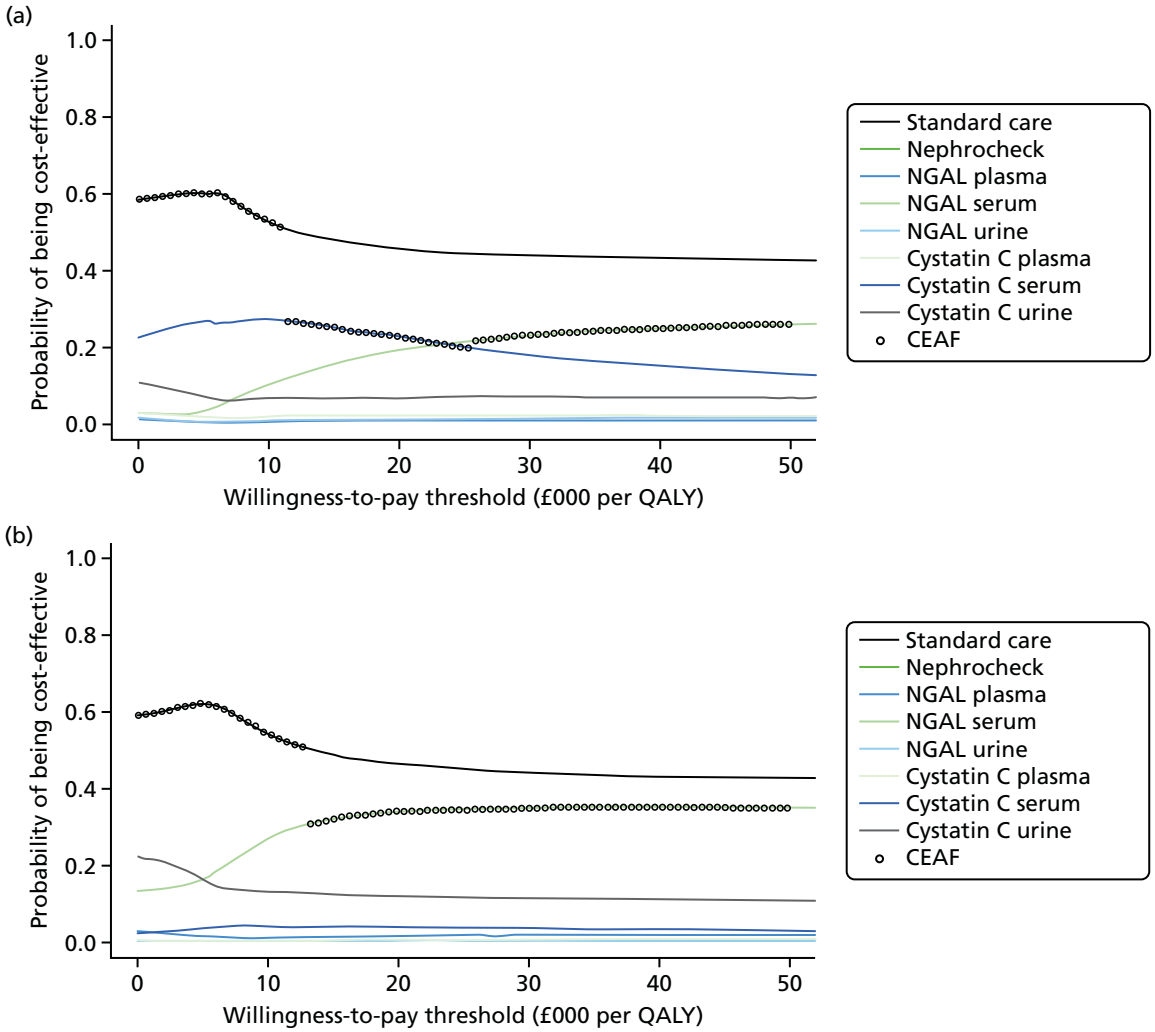

FIGURE 41 Cost-effectiveness acceptability frontier: (a) multiway base-case analysis; (b) multiway secondary analysis (post cardiac surgery).

perspective using individual patient trial data and information from the current literature. The primary analysis concerned the use of the tests in an all-comer ICU population; a secondary analysis was conducted to explore the impact of the tests on a subgroup of patients in the ICU post cardiac surgery.

In the primary analysis, based on the mean expected cost and QALY results only, each of the tests was cost-effective when compared in two-way analyses against standard care. Lifetime incremental QALYs ranged from 0.0115 [cystatin C (urine)] to 0.016 (Nephrocheck) and additional costs ranged from £149 [cystatin C (urine)] to £301 (Nephrocheck). The ICERs ranged from £11,476 to £13,504 per additional QALY for the cystatin C tests and from £13,372 to £13,828 for the NGAL tests; for Nephrocheck the ICER was £19,324. The corresponding INB values ranged from 0.001 QALYs for Nephrocheck to 0.006 QALYs for cystatin C (serum).

There is significant uncertainty around both the incremental cost results and the QALY results, leading to large uncertainty around the expected cost-effectiveness of the tests. For the incremental costs, all of the testing strategies had 95% CIs ranging from –£1000 to +£1400 and, for the incremental QALYs, all of the results ranged from –0.16 to +0.19 or +0.20. Compared with standard care alone, the probability that the tests are more effective than standard care was 56% for the cystatin C tests, 56–57% for the NGAL tests and 57% for Nephrocheck. The probability that the tests would be cost saving was 32% for Nephrocheck, 37–40% for the NGAL tests and 40–42% for the cystatin C tests. At a £20,000 per QALY threshold, the overall probability that the tests are cost-effective compared with standard care was 48% for Nephrocheck,

TABLE 63 Multiway incremental cost-effectiveness results (secondary analysis)

Strategy	Total cost (95% CI) (£)	Total QALYs (95% CI)	Comparator[a]	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (£)	Exclusion reason	ICER vs. standard care (£)
Standard care	29,959 (22,738 to 37,726)	6.5048 (0.56 to 10.20)	–	–	–	–	–	–
Cystatin C (urine)	30,082 (22,816 to 37,856)	6.5116 (0.56 to 10.21)	Standard care	124 (–908 to 1162)	0.0068 (–0.13 to 0.14)	18,076	Extendedly dominated by NGAL (serum)	18,076
NGAL (plasma)	30,096 (22,836 to 37,867)	6.513 (0.56 to 10.21)	Standard care	137 (–895 to 1178)	0.0082 (–0.13 to 0.14)	16,709		16,709
NGAL (serum)	30,108 (22,845 to 37,892)	6.5163 (0.56 to 10.22)	Standard care	149 (–905 to 1204)	0.0115 (–0.13 to 0.15)	13,051	–	13,051
Cystatin C (serum)	30,111 (22,847 to 37,869)	6.5148 (0.56 to 10.21)	NGAL (serum)	3 (–110 to 129)	–0.0015 (–0.01 to 0.01)	–2145	Dominated by NGAL (serum)	15,337
Cystatin C (plasma)	30,125 (22,879 to 37,889)	6.5129 (0.56 to 10.21)	NGAL (serum)	17 (–138 to 205)	–0.0033 (–0.02 to 0.01)	–5120		20,435
NGAL (urine)	30,131 (22,885 to 37,900)	6.5137 (0.56 to 10.21)	NGAL (serum)	23 (–116 to 194)	–0.0025 (–0.02 to 0.01)	–9050		19,287
Nephrocheck	30,163 (22,893 to 37,942)	6.5158 (0.56 to 10.20)	NGAL (serum)	55 (–43 to 154)	–0.0004 (–0.01 to 0.01)	–123,202		18,617

a In the multiway incremental analysis, for each test, after ranking strategies in order of increasing costs, the incremental cost and QALYs are calculated based on a comparison with the next best strategy, excluding any dominated or extendedly dominated options (i.e. excluding the shaded rows).

51–52% for the NGAL tests and 52–54% for the cystatin C tests. Raising the threshold value to £50,000 per QALY only slightly increased these probabilities.

The results of the multiway analysis indicate that, in the base case, between a threshold of £11,400 and a threshold of £25,400, cystatin C (serum) is the most cost-effective strategy, with a probability of cost-effectiveness of 23% at a £20,000 per QALY threshold. Above a £25,400 per QALY threshold, NGAL (serum) is expected to be the most cost-effective strategy, with a probability of cost-effectiveness of 20%. All other strategies either are found to be dominated by cystatin C (serum) or, in the case of Nephrocheck, have an ICER well above £20,000 per QALY [£12,855,101 compared with the next best alternative of NGAL (serum)]. This analysis suggests that, when taking into account the additional health impact that alternative tests could provide, several of the tests may no longer be cost-effective options.

Similar results were observed in the secondary analysis (i.e. in the post-cardiac surgery subgroup). All of the incremental costs and QALYs were slightly reduced compared with the base case, with incremental QALYs ranging from 0.007 [cystatin C (urine)] to 0.012 [NGAL (serum)] and additional costs ranging from £124 [cystatin C (urine)] to £205 (Nephrocheck). The ICERs were £13,051–19,287 per additional QALY for the cystatin C tests, £15,337–20,435 for the NGAL tests and £18,617 for Nephrocheck, with INB values ranging from –0.0002 to 0.004 QALYs. Again, there was substantial uncertainty around these results; at a £20,000 per QALY threshold there was a 48–52% probability that the tests would be cost-effective. In the multiway incremental analysis, only NGAL (serum) remained after removal of dominated or extendedly dominated alternatives (ICER £13,051 vs. standard care; probability of cost-effectiveness 35% at a £20,000 per QALY threshold).

The base-case results were highly sensitive to changes in key model parameters. Scenarios that lead to the tests becoming non-cost-effective (ICER > £20,000 per QALY) included shortening the time horizon of the analysis, reducing the incidence of AKI in the ICU, decreasing the impact or increasing the cost of early AKI intervention, applying a mortality risk for patients with FP test results, applying a cost saving for patients with negative test results and increased mortality for FN cases and increasing the cost of the Nephrocheck test. The only scenarios in which the probability that the tests were cost-effective increased to > 60% were increasing the impact of early AKI intervention to ≥ 40% and ≥ 60% risk reductions for cystatin C and NGAL respectively and assuming that at least 25%, 25% or 50% of FP test results were in fact TP test results for Nephrocheck, NGAL and cystatin C respectively.

Discussion

Interpretation of results

The results of the economic evaluation require careful interpretation. When analysed individually against standard care, all of the tests appear to be cost-effective in the base case and all except cystatin C (plasma) are cost-effective in the secondary analysis, based on an analysis of the overall expected costs and QALYs. However, the differences in each of the expected costs and QALYs are small and largely uncertain, resulting in probabilities of cost-effectiveness around 50%. Such uncertainty strongly indicates that further research is required before an informed adoption decision can be made. Furthermore, it necessitates a cautious interpretation of the subsequent multiway analysis, in which all tests are considered within the same evaluation; because the differences in the expected costs and QALYs across each of the tests are small and uncertain, marginal changes in any of these values could result in different test rankings, rendering these results potentially spurious. Perhaps the only exception to this is the Nephrocheck test, which is associated with extremely large ICERs compared with the alternative testing strategies because it has similar expected QALY outcomes but relatively higher costs. Assuming that the accuracy of the Nephrocheck test is not expected to improve significantly compared with the alternative tests, then the only way that this test is likely to represent a cost-effective strategy is if the cost of the test (currently estimated at > £70) is reduced to be in line with that of other competitor tests (i.e. £14.98 for NGAL and £4.26 for cystatin C).

Sensitivity analyses

The cost-effectiveness results are sensitive to changes in key parameters in the model. Most notably, all of the tests were sensitive to parameters related to the expected change in patient management and outcomes resulting from a positive or negative test result:

- *The cost and impact of early AKI intervention resulting from a TP test result*. It is assumed that patients with a TP test result can benefit from some form of early AKI intervention; however, the exact nature of this intervention is unclear because of the fact that treatment for AKI currently relies on a heterogeneous and non-specific bundle of interventions. No diagnostic outcome studies that could inform an estimation of the impact of such early intervention on patient outcomes have yet been conducted. As such, data on the impact of early nephrologist consultation on AKI incidence in a population of Mexican patients treated post cardiac surgery were used as a proxy.[464] The appropriateness of this estimation is unclear and the model results were highly sensitive to both the expected impact of treatment on AKI risks and the cost of the intervention. Reducing the impact of early AKI intervention to a 10% AKI risk reduction or increasing the cost of the intervention to £500 (around the 90th percentile of the base-case cost distribution) results in the Nephrocheck test no longer being cost-effective, whereas reducing the risk reduction to 5% or increasing the cost to £800 (around the 95th percentile) results in all tests no longer being cost-effective. In contrast, increasing the risk reduction or reducing the intervention cost leads to significant increases in expected cost-effectiveness and the probability of cost-effectiveness of all of the tests.
- *The impact of a FP test result*. In the base case it was assumed that no harm would result from a FP test result. Assuming instead that patients with a FP test result would incur a mortality impact (e.g. as a result of delayed access to necessary nephrotoxic agents) leads to reductions in the expected cost-effectiveness of the tests: a $\geq$ 5% mortality impact results in the Nephrocheck test no longer being cost-effective, a $\geq$ 10% mortality impact results in NGAL testing no longer being cost-effective and a $\geq$ 30% mortality impact results in cystatin C testing no longer being cost-effective.
- *The impact of a negative test result*. In the base case it was assumed that a negative test result (either TN or FN) would have no impact on baseline treatment costs or QALYs. However, it is reasonable to assume that this may not be the case: a negative result may lead to reduced costs as a result of reduced patient monitoring and/or may result in harm for FN cases because of that same reduced monitoring. Sensitivity analysis indicates that if a one-off cost saving of £100 is applied to all negative results, and a 10% increased ICU mortality rate is applied to FN results, this would lead to all testing strategies becoming cost saving at the expense of producing fewer QALYs, resulting in all strategies no longer being cost-effective. Note that, in the absence of any data, these values were chosen purely arbitrarily.

Other parameters that were found to be influential in the sensitivity analysis include:

- *The time horizon of the analysis*. Nephrocheck becomes cost-effective only if using a $\geq$ 20 year time horizon and cystatin C and NGAL become cost-effective only when using a $\geq$ 10-year time horizon. This indicates the importance of downstream health impacts (as a result of reduced CKD incidence and increased survival) relative to the short-term costs and health impacts in the model.
- *The incidence of AKI in the ICU*. Reducing the incidence of AKI diminishes the opportunity for tests to improve patient outcomes (as the absolute proportion of TP cases is reduced) while at the same time increasing the relative cost of unnecessary testing. The impact of this appears to be greatest for the two most expensive tests: decreasing the AKI incidence to $\leq$ 20% results in Nephrocheck no longer being cost-effective, whereas decreasing the AKI incidence to 10% results in NGAL testing no longer being cost-effective (in contrast, cystatin C testing remains cost-effective throughout). Thus, the tests are less likely to be cost-effective when few cases of AKI are expected. This may not be a common occurrence within the UK ICU setting, where recorded rates of AKI are generally high. It may be more relevant in settings in which patients entering ICU may be less acutely ill because of higher critical care capacities, resulting in patients having an overall lower risk of AKI.
- *Adjusting the test accuracy to account for the imperfect reference test*. Assuming that a proportion of FP test results are actually TP cases has a huge impact on the results. For example, recoding 10% of FP

cases in NGAL and cystatin C testing, or 25% of FP cases in Nephrocheck testing, leads to ICERs of < £10,000; recoding 25% of FP cases results in all tests having a ≥ 60% probability of being cost-effective. The interpretation of this analysis depends on how much we are willing to believe that FP cases may actually be TP cases, as a result of the known deficiencies in standard care testing. We are not aware of any current evidence that could inform this expectation, thus this analysis should be considered purely exploratory. It does, however, highlight the importance of the methodological issue of how to account for bias in estimates of diagnostic accuracy resulting from the use of imperfect reference tests; although there is a growing body of methodological research in this area, the focus to date has been on methods that require access to individual-level data (which have limited application in this kind of study in which the main source of evidence is aggregate secondary data), and we are not aware of any work that has been conducted from a health economic perspective. This is, therefore, a key area for future research.

In general, of the three tests evaluated in the sensitivity analyses, Nephrocheck was the most sensitive to changes in key parameters, whereas cystatin C testing was the most resilient to parameter changes. Nevertheless, all of the tests were found to be sensitive to the key parameters listed above, indicating the need for further research across these areas. As the results of the VOI analysis provide further insight into the relative importance of the different areas of uncertainty, full research recommendations are discussed in *Chapter 6*.

Previous economic evaluations

Our review of economic decision models identified two previous economic evaluations of biomarkers for the early identification of AKI in the critical care setting. Both of these studies found that testing strategies were a cost-effective addition to standard care. However, there are notable differences in the overall and incremental cost and QALY outcomes between these studies and our analysis. In the study by Shaw *et al.*[205] (the most comparable study, which also considered a UK adult ICU population), the authors reported a mean lifetime cost of £4672 and 11.79 QALYs for standard care in a post-cardiac surgery population, whereas, in the current equivalent analysis, we expect a mean lifetime cost of £29,959 and 6.50 QALYs. A key reason for the lower cost in the study by Shaw *et al.*[205] is because the authors did not include any follow-up costs for patients post hospital discharge, which are expected to be significant (starting at > £6000 per year) based on a recent large cohort study.[457] Other key differences include the fact that the previous analysis assumed lower ICU length of stays and mortality, did not account for utility in the ICU (which was negative in the current model) or hospital, did not include a follow-up mortality risk post ICU discharge and did not include an elevated cost for ESRD (separate from that for CKD). We therefore believe that it is highly likely that previous assessments of the long-term costs and QALYs for patients treated in the ICU have been under- and overestimated respectively.

Shaw *et al.*[205] found that urinary NGAL testing dominated standard care, being more effective and less costly. This is in contrast to the current analysis in which the same test was associated with an additional cost of £172 and an increase in QALYs of 0.009, resulting in an ICER of £19,287 and a 48% probability of being cost-effective. Again, there are key differences between the studies that we believe are driving these alternative results. In particular, the analysis in the study by Shaw *et al.*[205] considered four sequential NGAL tests and assumed that test accuracy was independent of the sequence of the tests, which is likely to increase the overall accuracy of the tests. In addition, it appears that all patients with TP results were assumed to benefit from early AKI treatment, regardless of the concurrent standard care test results (in contrast we assumed that only patients without a concurrent diagnosis of moderate/severe AKI would be able to benefit from early AKI treatment in the testing strategies). Finally, Shaw *et al.*[205] reported limited details of the distributional assumptions applied in their probabilistic analysis and so it is unclear if uncertainty in the model parameters has been fully captured.

Overall, although all three economic evaluations of biomarkers for the early diagnosis of AKI in the ICU to date indicate that tests may be cost-effective, we believe that our analysis more accurately reflects the expected costs and QALYs associated with these strategies and, most importantly, more accurately depicts the level of uncertainty around these decisions.

Generalisability

This study has evaluated Nephrocheck, NGAL and cystatin C tests for the early identification of AKI within both a general all-comers ICU population and a post-cardiac surgery subgroup population. Based on the fact that this is an early analysis, with the results of the sensitivity analysis indicating that the results are sensitive to changes in key parameters including the incidence of AKI and the impact of early treatment, it is unlikely that these results can be extrapolated to the use of tests across other settings (e.g. the hospital ward or the community). In addition, as many of the costs are specific to the UK NHS, generalisability beyond the UK should also be considered with caution.

Although each of the three tests was shown to be cost-effective compared with standard care, there is significant uncertainty around the results, as highlighted by the wide distribution of the incremental costs and QALYs, the relatively low probabilities of cost-effectiveness and the sensitivity of the results to changes in key parameters. The potential value of future research as a means of reducing this uncertainty is explored further in *Chapter 6*.

It should be noted that combining CKD stages 1–4 was considered to be a necessary simplification within the model. The key objective of the model was to capture any impacts related to the intervention (i.e. in this case, the tests). Based on expert consultation, it was not apparent that the tests and resulting treatments would have any significant impact on patient outcomes once CKD has developed. The CKD portion of the model therefore aimed to capture the most significant cost and QALY impacts associated with CKD, which were assumed to be the use of dialysis, the risk of ESRD and transplantation. This simplification is in line with previous models outlined in the review of AKI models.

Chapter 6 Research prioritisation

Introduction

A key objective of the AKI-Diagnostics project was to inform a strategy towards the generation of evidence leading to the adoption of diagnostics tests in critical care in a manner that maximises patient benefit and value for the NHS. Subject to demonstration of clinical efficacy, the final step of any diagnostic test towards adoption is a reimbursement decision based on cost-effectiveness. As such, a specific metric – VOI – has been chosen as the main determinant of research recommendations arising from the AKI-Diagnostics project.

Value of information analysis provides a pertinent framework for setting priorities for further research. This approach relies on the fact that resources that are spent on a new intervention will not be available to spend on alternative interventions: if we invest in a new intervention that is not the most cost-effective option, we could lose health (or money) that could have been gained if we had invested in a more cost-effective intervention. Research (i.e. the gain of more information) therefore has value if it reduces the risk of adopting an intervention that is not cost-effective. This value can be quantified as either lost health (measured in QALYs) or lost health-care resources (measured in monetary units) within the VOI framework. This chapter outlines the methods and findings of the VOI analysis conducted as part of the AKI-Diagnostics economic evaluation.

It is important to note that the VOI analysis presented here relies on multiple two-way comparisons between standard care and specific tests. This is on the grounds that the decision problem, in reality, includes more than just the three tests subjected to detailed study within the project. As such, a four-way comparison such as that presented in *Chapter 5* would be incomplete.

Methods

Value of information analysis

Value of information analysis was conducted for each of the shortlisted tests using the economic decision model outlined in *Chapter 5*. For the cystatin C and NGAL tests, which are available across multiple media (i.e. plasma, urine and serum), VOI analysis was conducted only for the individual test found to have the highest probability of being cost-effective based on the results of the CEA. This analysis therefore includes Nephrocheck, NGAL (plasma) and cystatin C (serum).

Within the VOI framework, several measures can be obtained to explore the impact of reducing uncertainty on the expected cost-effectiveness. The focus of this analysis was on the following measures:

- *Expected value of perfect information (EVPI)*. The EVPI represents the overall burden of uncertainty on the decision-maker for a defined decision. The economic model is used to determine the difference between the expected net benefit when a decision is made assuming perfect knowledge of all model parameters (estimated via model simulations assuming fixed input parameters sampling across the range of expected parameter values) and the net benefit under current uncertain information. The resulting EVPI provides an upper bound on the total amount that the decision-maker should be willing to invest in further research to eliminate all parameter uncertainty. A positive EVPI provides a *necessary* but *not sufficient* condition for the decision to invest in further research: a positive EVPI indicates that further research may be warranted; however, additional information including the expected cost of research, the likely reduction in uncertainty as a result of research and the opportunity cost of delayed adoption is required to make a definitive decision regarding future research requirements.

- *Expected value of perfect parameter information (EVPPI)*. The EVPPI is an extension of the EVPI in which the burden of uncertainty around particular individual parameters, or groups of parameters, is quantified.[480] The EVPPI indicates the maximum value that the decision-maker should be willing to invest to reduce all uncertainty around a specific parameter or group of parameters. As for the EVPI, the EVPPI presents a necessary but not sufficient condition for conducting further research. However, the EVPPI enables exploration of the key parameters driving the uncertainty, which can be used to inform the direction of further research.

Calculation of the VOI was conducted using non-parametric regression modelling approaches.[481,482] For single parameter EVPPI estimates and for groups of up to four parameters, regression was conducted using the generalised additive model. For parameter groups of five or above, the R 'earth' package was used, which utilises multivariate adaptive regression splines.[483]

To estimate the VOI for the total population of patients expected to be affected by an adoption decision, a baseline population of 258,956 was assumed, based on the reported number of critical care records in the 2014–15 Hospital Episodes Statistics report (adult critical care).[484] An annual discount rate of 3.5% was applied to this number over a 10-year time period, assuming that this is the time over which the decision would remain relevant (e.g. before a comparator intervention would be adopted). This results in a total 10-year discounted population of 2,229,012. All VOI statistics are expressed in monetary terms using the net monetary benefit statistic.

Results

Expected value of perfect information

The distribution of the EVPI across different willingness-to-pay thresholds for the Nephrocheck, cystatin C (serum) and NGAL (plasma) tests is shown in *Figures 42–44* respectively. At a willingness-to-pay threshold of £20,000 per QALY, the per-patient EVPI is £430 for Nephrocheck, £371 for NGAL (plasma) and £362 for cystatin C (serum). For the total 10-year discounted population of patients expected to be affected by this decision ($n = 2,229,012$), the corresponding 10-year population EVPI is £958M, £827M and £807M respectively. Population EVPPI for single model parameters, showing top ranked parameters only, is shown in *Figure 45*.

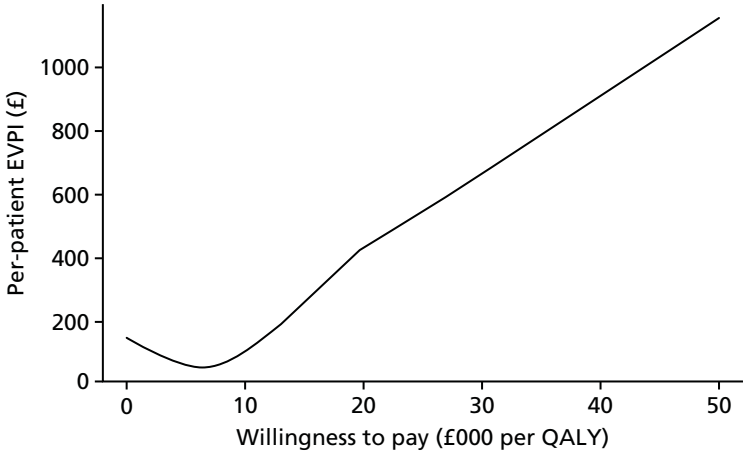

FIGURE 42 Expected value of perfect information: Nephrocheck vs. standard care.

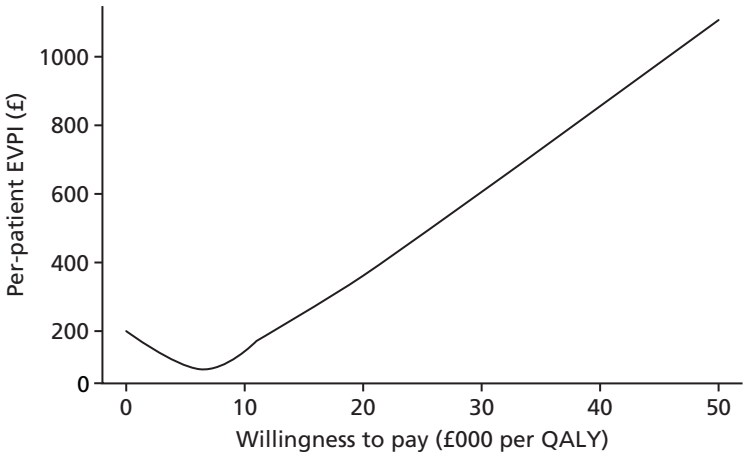

FIGURE 43 Expected value of perfect information: cystatin C (serum) vs. standard care.

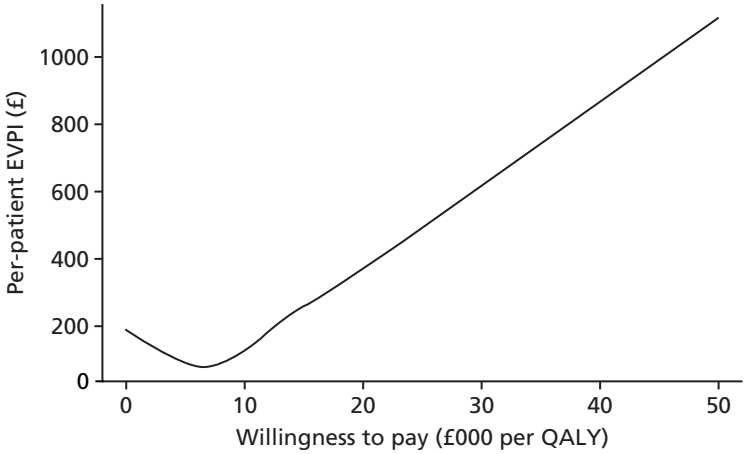

FIGURE 44 Expected value of perfect information: NGAL (plasma) vs. standard care.

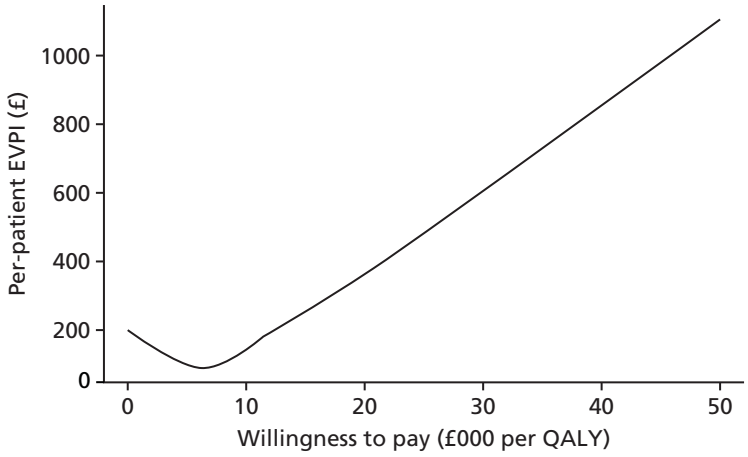

FIGURE 45 Population EVPPI for single model parameters (showing top ranked parameters only).

Expected value of perfect parameter information

The population EVPPIs for single model parameters are provided in *Figure 46*. For all tests the majority of top-ranked individual parameters relate to the proportion of patients arriving in the ICU with AKI, the proportion being diagnosed with AKI on the first day, the distribution of patients across health states at the end of the hospital period of the model and the impact of early AKI intervention on future AKI risks. Across all of the top ranked parameters shown, the Nephrocheck test is associated with the highest EVPPI, followed by the NGAL (plasma) test and the cystatin C (serum) test.

The population EVPPIs for groups of parameters are presented in *Figure 47*. The most influential groups of parameters are the incidence and starting stages of AKI, followed by the test parameters (test accuracy and impact and cost of early AKI intervention), and the starting distributions of patients entering the follow-up model (which are drawn from the end-state distribution of patients in the hospital period of the model). For all of the top-ranked parameter groups, the Nephrocheck test is associated with the highest VOI, followed by the NGAL (plasma) test and cystatin C (serum) test. The only parameter group for which this is not the case is ward mortality and discharge rates, for which NGAL (plasma) and cystatin C (serum) have positive EVPPIs (£1.53M and £0.48M respectively) and Nephrocheck has a zero value.

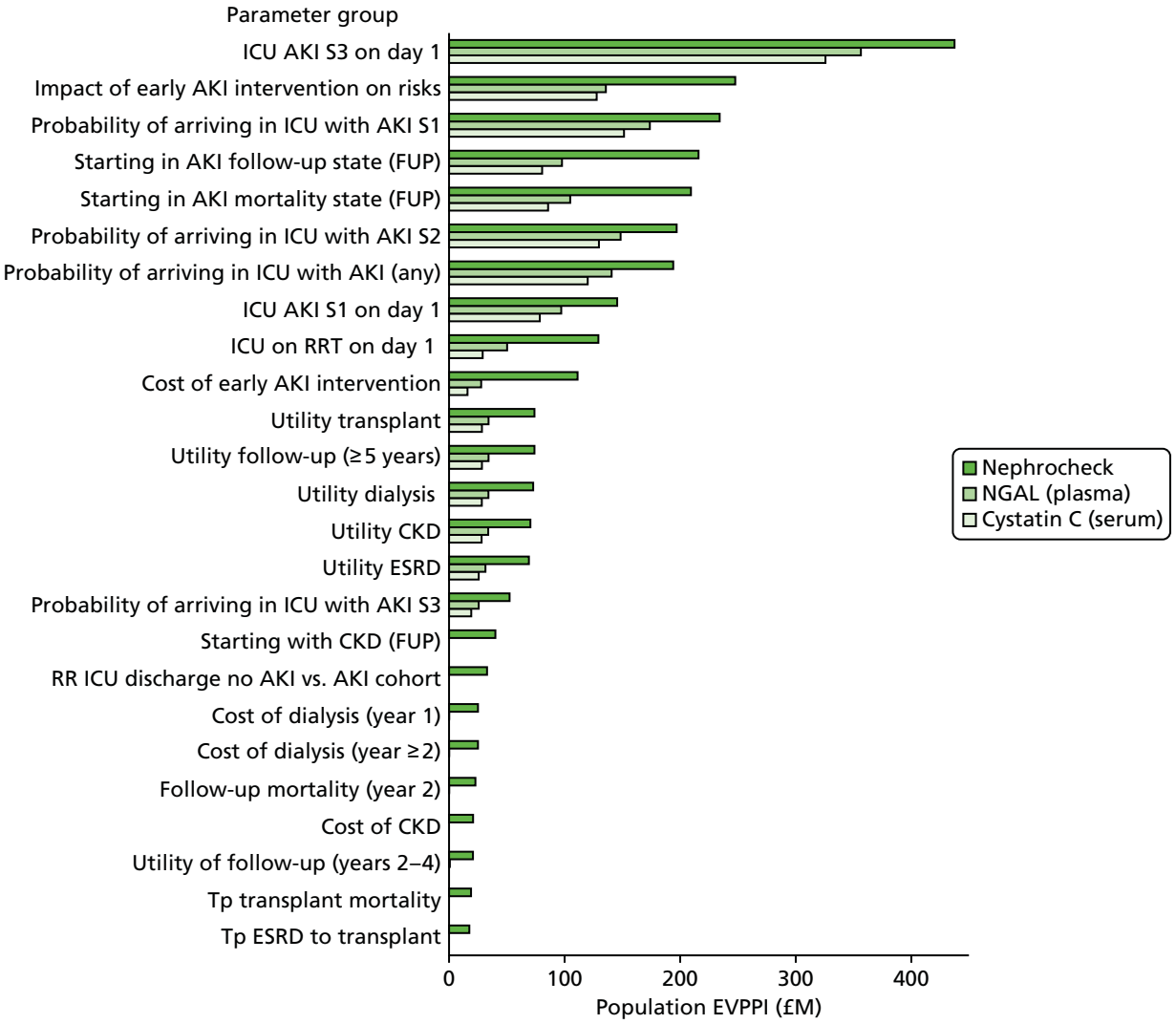

FIGURE 46 Population EVPPIs for single model parameters (showing top-ranked parameters only). FUP, follow-up period; Tp, transition probability.

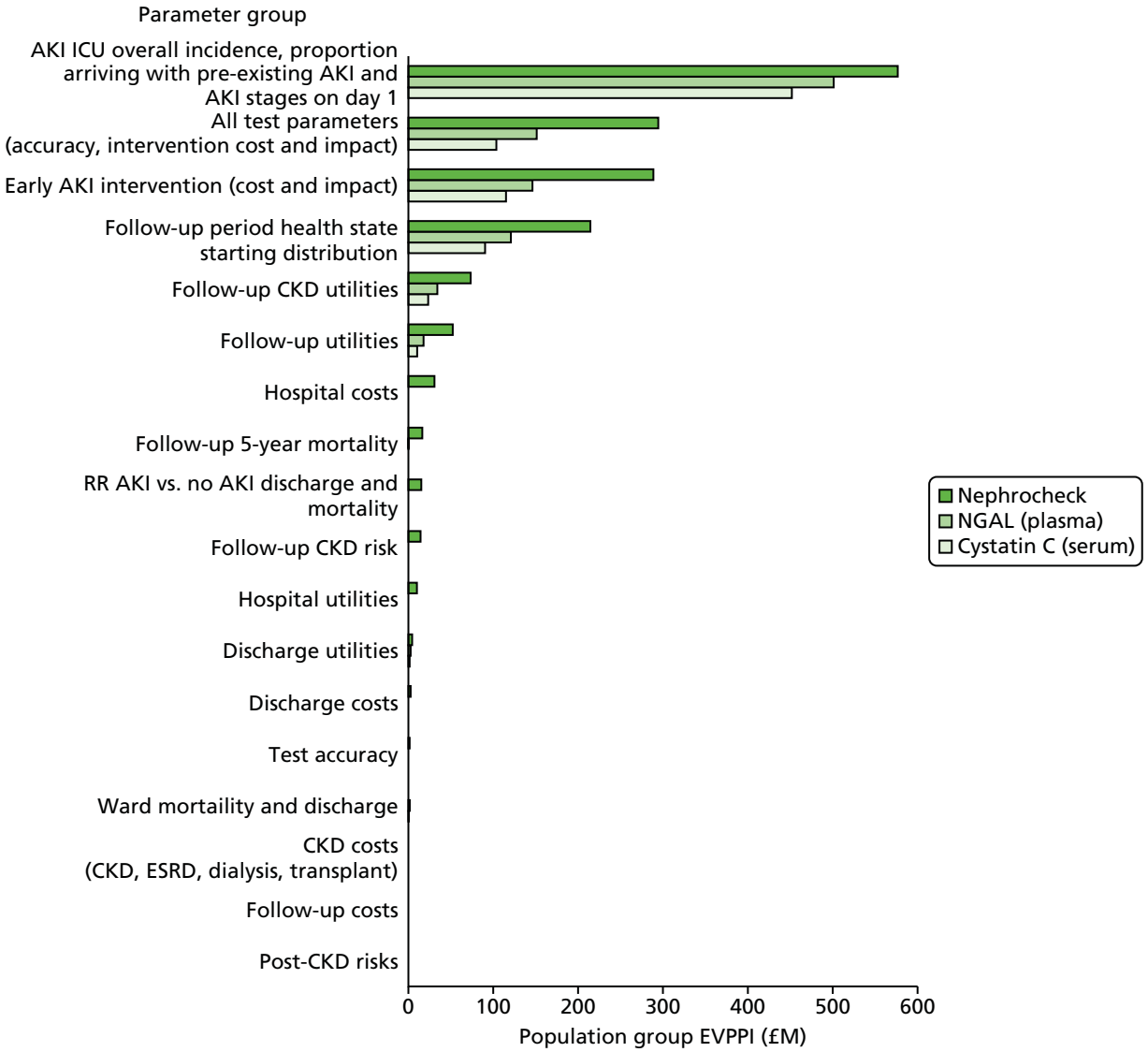

FIGURE 47 Population EVPPIs for parameter groups.

Summary

A VOI analysis was conducted to (1) inform a stop–go decision on further research into AKI diagnostic tests for the DEC programme and (2) guide the design of further research to ensure that it provides information that will reduce decision uncertainty in a targeted manner. Both the EVPI and the EVPPI metric were used to characterise the burden of decision uncertainty across and between the model parameters.

For the total 10-year discounted population of patients expected to be affected by this decision ($n = 2{,}229{,}012$), the 10-year population EVPIs are £958M, £827M and £807M for Nephrocheck, NGAL and cystatin C respectively. A positive EVPI is a necessary condition for further research being worthwhile, which has therefore been met for all three tests considered. Furthermore, the magnitude of these estimates suggests that the current burden of uncertainty puts us at significant risk of population health loss through an incorrect adoption decision.

When considering individual parameters, the top-ranked parameters in terms of population EVPPIs were the proportion of patients arriving in the ICU with pre-existing AKI, the proportion being diagnosed with AKI on the first day, the distribution of patients across health states at the end of the hospital period of the model and the cost and impact of early AKI intervention. Many of these values were > £100M.

When considering groups of parameters, the top-ranked EVPPIs (all also > £100M) were:

- the incidence and starting stages of AKI
- the impact and cost of early AKI intervention.

Discussion

Interpretation of the results and future research recommendations

The results of the VOI analysis indicate that there is a large population burden of decision uncertainty around the decision to reimburse the three tests that have been studied in detail. Conducting further research to reduce uncertainty around this decision problem is likely to be of high population value. In particular, two key areas for future research are highlighted as being particularly worthwhile: (1) the incidence and progression of AKI in the ICU and (2) the impact and cost of early AKI intervention. In the grouped EVPPI analysis, both of these parameter groups had values of > £100M across all three tests and ranked much higher than other parameters. This indicates that an investment of up to £100M would be worthwhile if it is able to eliminate uncertainty around these parameters. Although the test parameters grouping (composed of the test accuracy in addition to the impact and cost of early AKI intervention) also scored highly, it appears that this value is driven by the early AKI intervention parameters rather than the accuracy of the tests as these two group values are almost identical and the test accuracy parameters do not feature in the top-ranked single EVPPIs. It is also interesting to note that most of the top-ranked parameters relate to the short-term patient outcomes, suggesting that the downstream parameters are of less importance from the perspective of further research.

Although a formal RCT comparing a testing strategy with standard care would be necessary to provide definitive evidence for the clinical effectiveness and cost-effectiveness of the tests, these results suggest that expensive long-term follow-up may not be necessary. It may also be entirely possible to reduce our decision uncertainty substantially by undertaking some observational research to better understand the rates and trajectory of AKI in the ICU prior to undertaking a trial. It may even be possible to gain useful data from an observational study that looks at the use of the tests in real-world practice. This would enable valuable data to be gathered on how the tests may impact on clinical decision-making and change in the standard care pathway. It appears that, if knowledge is gained about these parameters, prominent sources of decision uncertainty could be addressed.

A single-centre study[485] in patients after cardiac surgery using the Nephrocheck test has recently been reported, indicating that such studies are feasible. Further multicentre studies, ideally evaluating multiple tests, will be required to inform a robust assessment of the long-term health economic impact of such tests. These could be cluster or individually randomised interventions based on the complexities of the final study protocols and any concerns about contamination. Appropriate arguments would also need to be developed for the rationale of consenting patients (or not) in this setting.

It should be noted that the EVPPI results provide an upper bound on the amount that a decision-maker should be willing to spend on this research; additional factors need to be considered such as the cost of research; to what extent uncertainty would be diminished; the impact of treating patients in a research setting; and the impact of delaying access to treatment for NHS patients not taking part in a study. To make more precise statements about the value of research, a calculation of the expected value of sample information (EVSI) would be necessary, which has not been undertaken within the constraints of this project. Nevertheless, the magnitude of the VOI estimates observed strongly indicates that the required research would be achievable within this maximum budget (i.e. £100M). In addition to this form of study, better data on the incidence and progression of AKI in the ICU will continually become available from the AKI registry (see *Chapter 5*) and could be used to update the current evaluation, with a likely significant impact on uncertainty.

The results from the sensitivity analyses in *Chapter 5* support these findings. In addition, the results of the sensitivity analyses also highlight the need for further evidence on the specific types of clinical management changes that would be implemented as a result of a positive or negative test result and the impact that they would have on patient short-term outcomes (i.e. not just limited to the impact of early AKI intervention for TPs). It appears that either a clinical consensus needs to be obtained here or the impact of alternative courses of action needs to be explored within a clinical study, which could be a fairly simple observational study. In addition, the meta-analysis of diagnostic studies could be extended to include a sensitivity analysis in which studies at high risk of bias are excluded. This would provide further information with respect to the robustness of estimates that are included in the economic evaluation.

Limitations

A key limitation of this analysis is the fact that the daily AKI transition probabilities could not be included as parameters of interest in the EVPPI analysis because of the size of these parameter matrices (which results in the VOI analysis taking an impractical amount of time to run, even using substantial parallel computing resources). However, the incidence of AKI, the proportion of patients with pre-existing AKI, the distribution of AKI on the first day and the end-state distribution of patients in the hospital period of the model all feature highly in the single- and grouped-parameter EVPPI analyses. It appears safe therefore to assume that the daily transitions between AKI states would similarly feature in the top-ranked parameters.

In addition to the EVPI and the EVPPI, the EVSI can be computed to determine the value of a defined research proposal, that is, a clinical trial of specified length and size that would provide information on specific parameters. EVSI calculation remains computationally expensive and was therefore not explored in this analysis but would be a useful addition if specific future study designs are proposed.

Chapter 7 Discussion

The AKI-Diagnostics project had the ambitious goal of establishing a recommended research and development strategy for diagnostic tests for AKI in critical care in the UK. This was undertaken within the NIHR DEC programme in acknowledgement that this is an area of significant health burden and is significantly underdeveloped as an area of technological application. As the first FDA-approved test, there was a risk that the Nephrocheck test would undergo widespread adoption without consideration of a robust evidence development strategy comparing it with other testing options and without it going through the necessary safeguard of a national health technology assessment.

The key clinical message from the project is that diagnostic tests for AKI in critical care patients who do not have AKI on admission have the potential to provide a meaningful albeit small benefit to patients. Although the number of studies supporting the Nephrocheck test is considerably smaller than those supporting the NGAL and cystatin C tests, the quality of these studies does appear to be high when faced with formal critical appraisal, particularly with regard to aspects of analytical validity.

All tests may represent strategies that may be cost-effective, but this is subject to uncertainty, which is particularly driven by assumptions regarding the impact of a diagnostic test on clinical care and the resulting change in clinical outcomes. Although these factors are both modelled in detail in the economic model, observational or experimental studies are required to ratify the link between possible care process changes and AKI rates and their longer-term implications.

The results of this project may be interpreted by some as providing sufficient evidence for adoption of the tests in the NHS; however, we would recommend that this is undertaken only within the framework of careful observational study, audit and an exit strategy at the point of evidence re-evaluation. Such an approach would allow many of the assumptions on which the economic model relies to be tested or better informed by data. There is interest by national reimbursement decision-makers such as NICE in new models of reimbursement that introduce conditionality on a positive reimbursement decision. We consider AKI diagnostic tests to be an ideal test case for such a model. There is interest by national reimbursement decision-makers such as NICE in new models of reimbursement that introduce conditionality on a positive reimbursement decision. We consider AKI diagnostic tests to be a suitable test case for such a model. This could be achieved by clearly defining the indication and putting in place a prospective audit framework that captures key data items that are currently uncertain or absent from the economic model.

The methods for quantitatively establishing an evidence-based and value-based research and development strategy for diagnostic testing are not established in a universally accepted or methodologically adequate manner. As such, the AKI-Diagnostics project represents a methods experiment that brings together many evaluation components. The structure of this report is intended to separate these components into their own sections for clarity, while acknowledging that they are interlinked and co-dependent. Most components ultimately feed into the economic model and this can be considered the summarising output from the project. The limitations of the individual components are discussed in detail in the individual chapters. It should be noted that, although our consideration of analytical validity goes further than what is normally required by health technology assessment authorities, the uncertainties around analytical validity parameters are not captured within the economic model and, therefore, do not feature in the VOI analysis. Development of improved methods for the incorporation of analytical validity in economic models should be considered an additional priority for further research.

Many learning points have emerged and will inform the design and conduct of similar attempts to map out a research strategy for the DECs and the wider NIHR in other diseases or scientific areas of study. The horizon scan identified a very large long list of candidate biomarkers and tests. We employed a ranking system based on numbers of publications, the combined sample size and mechanism of action, combined with expert opinion, using this as a surrogate for trajectory and novelty. Based on this ranking, we focused

on three tests for detailed study, consuming the remaining resources available within the AKI-Diagnostics project. It is unknown to us whether these three tests represent the best options for further research investment compared with the many other putative tests that also require detailed study. Indeed, our relatively crude ranking strategy may specifically have missed novel or upcoming tests that have appeared only recently in the literature. We feel that further investment in methodology research to improve the methods for horizon scanning and the ranking of new technologies for public sector research investment would be very worthwhile.

There were two important limitations in the meta-analysis of sensitivity and specificity, the most important of which was the issue of an imperfect reference standard for an AKI definition based on urine output and serum creatinine; the other limitation was the issue of heterogeneity between studies, particularly with regard to the choice of case definition threshold. Our ability to explore both of these issues was severely hampered by a lack of data, particularly for NGAL and cystatin C, for which, despite a large volume of published studies, reporting standards were simply inadequate in the large majority for this purpose. We attempted to look at the potential impact of an imperfect reference standard in a fairly crude way using the economic model. In this analysis we showed that, if it is assumed that $\geq 25\%$ of the FP results are actually TP results, tests have the potential to be notably more cost-effective (ICERs of <£10,000 per QALY and $> 60\%$ probability of being cost-effective). There should therefore be a strong incentive for researchers and manufacturers to study this further.

Several issues emerged during the construction and analysis of the economic model and the establishment of the clinical pathway on which it relies. A key challenge for the project was modelling the clinical impact and consequent outcomes from the results of the diagnostic tests. In the AKI-Diagnostics economic model these were derived from the confusion matrix, which allocates simulated patients as TPs, TNs, FPs and FNs. For the TP results we assumed that, for patients with early AKI, patients will benefit from some form of early AKI intervention, but the exact nature of this intervention is unclear because treatment for AKI currently relies on a non-specific bundle of 'treatments'. No studies were available to inform the nature or impact of such early intervention on patient outcomes and as such we have had to use data on early nephrologist consultation as a proxy, with substantial uncertainty around the impact and cost of this intervention. All of the sensitivity and VOI analyses strongly indicate that the results are highly sensitive to changes in these parameters. Furthermore, we do not know what impact this early intervention would have on FP cases. It is also unclear if any management changes will result from a negative test result. In the base-case analysis we assumed no impact for FP or for all negative test results; however, it is completely reasonable to assume that this may not be the case. For example, FP results may result in harm because of delayed access to necessary treatments, whereas negative results may result in cost savings because of reduced monitoring costs and FN results may result in harm because of that same reduced monitoring. Again, the sensitivity analyses indicate that uncertainty in the impact of early intervention would have a significant impact. More information on all of these factors is needed if we want to make an informed adoption decision. In the face of emerging pharmaceutical treatments, further analysis could use the AKI-Diagnostics model to evaluate the potential cost-effectiveness of new drugs for AKI in light of hypothesised treatment effect sizes.

Uncertainty around the incidence and movement of patients between AKI stages in the model is another key driver of uncertainty. Our decision to model the transition of patients between AKI stages on a daily basis is data intensive, but we consider this level of detail to be necessary because of the importance of this time period in the natural history of AKI in a critical care setting. At the time of analysis, data from only 60 patients were available from the AKI registry. As time passes, a greater number of data will become available from the AKI registry and should help resolve much of this uncertainty.

A number of future research recommendations may build on or expand the work of the AKI-Diagnostics project. These include (1) a repeat meta-analysis excluding studies at high risk of bias and (2) testing the reliability and validity of the framework for assessing the quality of analytical validity studies.

We propose that biomarkers will help us stratify the many different types of AKI and better understand the underlying pathophysiology. A better understanding of the pathophysiology and the identification of the progression of functional AKI, in which there is no tubular damage, to tubular damage will further our ability to target therapies appropriately. We propose that we already have the capacity to introduce care pathways for patients with AKI and that some of the significant issues that we experience with this patient group relate to the delay in recognition of the condition. With regard to elevated creatinine values, some of this delay is associated with the transfer of data from the laboratory to the practitioner. However, even if the time delay associated with this pathway was reduced to a minimum the serum creatinine level would still represent a delayed marker that does not distinguish between functional AKI and damage AKI and does not indicate the severity of the damage. The early recognition by a biomarker of damage occurring in the kidney will trigger a clinical review for signs of sepsis, the avoidance of toxins, for example intravenous iodinated contrast and non-steroidal anti-inflammatory drugs, and a more robust response in terms of volume assessment, fluid replacement and consideration for the use of vasopressors. This would represent a personalised approach to a patient identified as developing AKI and it would be anticipated that this would reduce the injury and the chances of progression from early injury to more severe injury, with the associated increased risks of morbidity and mortality. Looking to the future it is hoped that, through the identification of new biomarkers that are able to distinguish tubular injury in the kidneys from functional AKI without kidney injury having yet occurred, therapies could be studied that target the underlying pathophysiological processes.

It may be considered that there will be no immediate added value to clinical practice from the AKI-Diagnostics project; however, this project has provided a comprehensive overview of work that has already been performed on biomarkers and, importantly, what work needs to be carried out going forward for them to be of clinical utility. There is a great deal of literature on these biomarkers and there is much confusion about their applicability in the NHS and outside in the global health-care community. This report has provided a summary of what is currently understood about the clinical utility of three high-profile biomarkers. We are regularly asked by clinical colleagues if and how we should utilise biomarkers in the critical care unit. We think that this report urges caution in investing in new biomarkers until the correct studies have been carried out that link the use of a particular biomarker with a clinical care pathway, so that its effect on patient outcomes through a plausible mechanism of clinical impact can be investigated.

Going forward, the development of a fit-for-purpose economic decision model in the AKI-Diagnostics project has provided a platform for the DECs and the NIHR to further develop a UK research strategy in this area. With relatively little funding, extra tests or biomarkers could be reviewed and evaluated in the economic model. It would also be possible to investigate tests used in settings beyond the immediate admission period to look at risk stratification or sequential monitoring. It is entirely possible that companies or academic institutions that wish to further evaluate in-development tests may take advantage of the opportunity presented by building on the work of the AKI-Diagnostics project or it may be that NICE or other national decision-makers wish to fund the evaluation of tests when they emerge from their respective pipelines.

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Peter S Hall (Senior Clinical Lecturer) was the methods lead and provided expertise in health economics.

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Michael Messenger (Deputy Director of the NIHR DEC Leeds, Healthcare Scientist) was the lead for performance measurement.

Michelle Hutchinson (Biostatistician) was the project statistician.

Judy Wright (Senior Information Specialist) was the lead for the search strategies.

Karen Vinall-Collier (Research Fellow) was the lead for the qualitative methods and project co-ordination.

Claire Corps was the patient representative on the study.

Patrick Hamilton (Clinical Research Fellow) was the advising nephrologist.

David Meads (Senior Lecturer in Health Economics) was the supervising health economist.

Andrew Lewington (Consultant Nephrologist) was the clinical lead and provided expertise in nephrology.

Publications

Mitchell E, Smith A, Wright J, Calder N, Wickramasekera N, Messenger M, *et al. Review Strategies to Inform Research Prioritization of Biomarkers: AKI-Diagnostics Case Study*. Methods for Evaluating Medical Tests and Biomarkers Symposium, Birmingham, 2016 (abstract).

Smith A, Hall P, Meads D, Hutchinson M, Mitchell E, Wright J, *et al. Cost-effectiveness of NephroCheck® for Acute Kidney Injury in Critical Care*. American Society of Nephrology Annual Conference, Chicago, 2016 (abstract).

Mitchell E, Smith A, Wright J, Calder N, Wickramasekera N, Messenger M, *et al. Diagnostic Accuracy of the NephroCheck Test for Acute Kidney Injury in Critical Care: Systematic Review and Meta-analysis*. American Society of Nephrology Annual Conference, Chicago, 2016 (abstract).

Smith A, Hall P, Meads D, Hutchinson M, Mitchell E, Wright J, *et al. Using Cost-effectiveness and Value of Information Analysis to Inform Research Prioritisation: Findings from the AKI-Diagnostics Study*. iHEA, London, 2017 (abstract).

Data sharing statement

As a secondary research project, no data are available for sharing; however, the corresponding author will consider requests to share the model programming code.

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Appendix 1 AKI-Diagnostics search strategies: search 1 – horizon scanning

ClinicalTrials.gov (via the US National Institutes of Health)

Searched 29 September 2014.

1. biomarker* or marker* l acute kidney injury (89)
2. identify l acute kidney injury (20)
3. diagnose l acute kidney injury (70)
4. prognosis l acute kidney injury (15)
5. detect l acute kidney injury OR acute renal injury (15)
6. predict l acute kidney injury OR acute renal injury (27)
7. monitor l acute kidney injury OR acute renal injury (2)
8. stratify l acute kidney injury OR acute renal injury (2)
9. accuracy l acute kidney injury OR acute renal injury (12)
10. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9

Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 9 of 12, September 2014)

Searched 29 September 2014.

Search strategy

#1 Biomarker* or 'bio* marker*' or test or tests or factor or diagnostic*:ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Biological Markers] explode all trees

#3 MeSH descriptor: [Acute Kidney Injury] explode all trees and with qualifier(s): [Diagnosis - DI]

#4 MeSH descriptor: [Acute-Phase Proteins] explode all trees and with qualifier(s): [Diagnostic use - DU]

#5 MeSH descriptor: [Insulin-Like Growth Factor Binding Proteins] explode all trees and with qualifier(s): [Diagnostic use - DU]

#6 (NGAL or 'Neutrophil gelatinase-associated lipocalin' or 'lipocalin 2' or lcn2 or 'TIMP-2' or 'TIMP 2' or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2' or KIM-1 or TIMD1 or 'TIM-1' or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1' or Cystatin C or 'Cystatin C' or L-FABP or (Liver near/2 'Fatty acid-binding protein') or 'IL-18' or 'IL 18' or Interleukin-18 or 'Interleukin 18' or MIOX or 'myo-inositol oxygenase' or NTN1 or 'netrin-1' or IGFBP7 or IBP-7 or 'IGF-binding protein 7' or 'Insulin-like growth factor-binding protein 7' or potassium or Creat or Crea or creatinine or 'T Prot' or 'Total Protein' or 'Acute-Phase Protein*' or Alb or Albumin or BUN or 'Blood Urea Nitrogen' or AAP or 'AP-N' or hAPN or AP-M or 'EC=3.4.11.2' or 'microsomal aminopeptidase' or 'Alanine aminopeptidase' or 'ALP-1' or GCAP or 'PLAP-like' or 'Alkaline phosphatase' or 'Alkaline phosphatase' or 'placental-like' or GST or 'glutathione transferase' or 'glutathione-S-transferase' or 'Glutathione S-transferase A2' or 'EC = 2.5.1.18' or 'GGT 5' or GGT5 or 'gamma glutamyltransferase' or 'gamma glutamyl transferase' or 'glutamyl transpeptidase' or ('N-acetyl' near/2 glucosaminidase) or 'n acetylglucosaminyltransferase' or 'n acetylglucosamine' or 'histone acetyltransferase' or 'Bifunctional protein*' or ncoat* or NAG or OGA or

microglobulin or AMBP or 'retinol binding protein 4' or 'plasma retinol binding protein' or microalbumin or clusterin or 'Apo-J' or 'TRPM-2' or 'Cysteine-rich protein' or 'Cysteine-rich motor neuron 1 protein' or 'CYR-61' or 'CRIM-1' or 'SPP-1' or Osteopontin or NHE3 or NHE or 'exchanger 9B2' or 'exchanger isoform' or 'proton sodium exchange' or 'sodium proton exchange protein 3' or 'Alpha-2-HS-glycoprotein' or 'fetuin A' or Klotho or CALB1 or calbindin or 'h-FABP' or MDGI or 'M-FABP' or 'Fatty acid-binding protein' or renin or 'ec=3.4.23.15'):ti,ab,kw

#7 {or #1-#6}

#8 MeSH descriptor: [Acute Kidney Injury] explode all trees

#9 MeSH descriptor: [Kidney Tubular Necrosis, Acute] explode all trees

#10 MeSH descriptor: [Acute Disease] explode all trees

#11 MeSH descriptor: [Kidney Diseases] explode all trees

#12 #10 and #11

#13 (Acute near/3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)):ti,ab,kw (Word variations have been searched)

#14 (Acute near/3 (renal disease* or renal injury or renal failure or renal dysfunction)):ti,ab,kw

#15 ((Acute near/3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*'):ti,ab,kw

#16 (AKI):ti,ab,kw

#17 ('contrast induced nephropathy'):ti,ab,kw

#18 (renal or kidney* or nephr*):ti,ab,kw or {or #8-#17}

#19 (reperfusion near/5 (injur* or isch?emi*)):ti,ab,kw

#20 MeSH descriptor: [Reperfusion Injury] explode all trees

#21 ('delayed graft function*'):ti,ab,kw

#22 MeSH descriptor: [Delayed Graft Function] explode all trees

#23 {or #19-#22} and #18

#24 #23 or {or #8-#17} Publication Year from 2004 to 2014

#25 Sera or Serum or Serologic* or urine or urinary:ti (Word variations have been searched)

#26 sample* or specimen*:ti,ab,kw (Word variations have been searched)

#27 MeSH descriptor: [Analytic Sample Preparation Methods] explode all trees

#28 MeSH descriptor: [Blood Specimen Collection] explode all trees

#29 MeSH descriptor: [Urine Specimen Collection] explode all trees

#30 MeSH descriptor: [Specimen Handling] explode all trees

#31 plasma or blood or urine or urinary:ti,ab,kw (Word variations have been searched)

#32 MeSH descriptor: [Blood] explode all trees

#33 MeSH descriptor: [Blood] this term only

#34 MeSH descriptor: [Plasma] explode all trees

#35 MeSH descriptor: [Serum] explode all trees

#36 MeSH descriptor: [Urine] this term only

#37 ({or #31-#36} and {or #26-#30}) or #25

#38 MeSH descriptor: [Acute Kidney Injury] explode all trees and with qualifier(s): [Blood - BL, Urine - UR]

#39 MeSH descriptor: [Kidney Tubular Necrosis, Acute] explode all trees and with qualifier(s): [Blood - BL, Urine - UR]

#40 Any MeSH descriptor with qualifier(s): [Blood - BL, Urine - UR]

#41 #23 and #40

#42 {or #37-#39} or #41

#43 #42 and #24

#44 MeSH descriptor: [Biological Markers] explode all trees

#45 (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif* or accura* or marker* or biomarker* or sensitivity):ti,ab,kw (Word variations have been searched)

#46 {or #44-#45} and #43

#47 MeSH descriptor: [Animals] explode all trees

#48 MeSH descriptor: [Veterinary Medicine] explode all trees

#49 MeSH descriptor: [Animal Experimentation] explode all trees

#50 MeSH descriptor: [Humans] explode all trees

#51 {or #47-#49} not #50

#52 #7 and #46

#53 #52 not #51

Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 9 of 12, September 2014)

Searched 29 September 2014.

Same search as for Cochrane Central Register of Controlled Trials.

Conference Proceedings Citation Index – Science (via Thomson Reuters' Web of Science) (2008–present)

Searched 29 September 2014.

Search strategy

1. TS=('acute kidney injury' or AKI) OR TS=((Acute NEAR/3 ('kidney disease*' or 'kidney injury' or 'kidney failure' or 'kidney dysfunction'))) OR TS=((Acute NEAR/3 ('renal disease*' or 'renal injury' or 'renal failure' or 'renal dysfunction'))) OR TS=(((Acute NEAR/3 ('Tubular Necrosis' or nephrotoxic*)) or 'nephrotoxic injur*')) OR TS=('contrast induced nephropath*') OR TS=((reperfusion NEAR/5 (injur* or isch?emi*)) AND (renal or kidney* or nephr*)) OR TS=(('Delayed Graft Function') AND (renal or kidney* or nephr*))
2. TI=((Sera or Serum or Serologic* or urine or urinary)) OR TS=((sample* or specimen*) AND (plasma or blood or urine or urinary or serum or sera or serologic)) OR TS=(Urinalysis)
3. #2 AND #1
4. TS=(discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif* or accura* or marker* or biomarker* or sensitivity).
5. TS=(NGAL or 'Neutrophil gelatinase-associated lipocalin' or 'lipocalin 2' or lcn2 or 'TIMP-2' or 'TIMP 2' or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2' or KIM-1 or TIMD1 or 'TIM-1' or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1' or Cystatin C or 'Cystatin C' or L-FABP or (Liver NEAR/2 'Fatty acid-binding protein') or 'IL-18' or 'IL 18' or Interleukin-18 or 'Interleukin 18' or MIOX or 'myo-inositol oxygenase' or NTN1 or 'netrin-1' or IGFBP7 or IBP-7 or 'IGF-binding protein 7' or 'Insulin-like growth factor-binding protein 7' or potassium or Creat or Crea or creatinine or 'T Prot' or 'Total Protein' or 'Acute-Phase Protein*' or Alb or Albumin or BUN or 'Blood Urea Nitrogen' or AAP or 'AP-N' or hAPN or AP-M or 'EC=3.4.11.2' or 'microsomal aminopeptidase' or 'Alanine aminopeptidase' or 'ALP-1' or GCAP or 'PLAP-like' or 'Alkaline phosphatase' or 'Alkaline phosphatase' or 'placental-like' or GST or 'glutathione transferase' or 'glutathione-S-transferase' or 'Glutathione S-transferase A2' or 'EC=2.5.1.18' or 'GGT 5' or GGT5 or 'gamma glutamyltransferase' or 'gamma glutamyl transferase' or 'glutamyl transpeptidase' or ('N-acetyl' NEAR/2 glucosaminidase) or 'n acetylglucosaminyltransferase' or 'n acetylglucosamine' or 'histone acetyltransferase' or 'Bifunctional protein*' or ncoat* or NAG or OGA or microglobulin or AMBP or 'retinol binding protein 4' or 'plasma retinol binding protein' or microalbumin or clusterin or 'Apo-J' or 'TRPM-2' or 'Cysteine-rich protein' or 'Cysteine-rich motor neuron 1 protein' or 'CYR-61' or 'CRIM-1' or 'SPP-1' or Osteopontin or NHE3 or NHE or 'exchanger 9B2' or 'exchanger isoform' or 'proton sodium exchange' or 'sodium proton exchange protein 3' or 'Alpha-2-HS-glycoprotein' or 'fetuin A' or Klotho or CALB1 or calbindin or 'h-FABP' or MDGI or 'M-FABP' or 'Fatty acid-binding protein' or renin or 'ec=3.4.23.15')
6. TS=(biomarker* or 'bio* marker*' or 'marker*') OR TS=(diagnostic or test or tests or factor)
7. #4 AND #3
8. #6 OR #5
9. #8 AND #7
10. TS= (rat or rats or swine or pigs or pig or mice or mouse) NOT TS=(human* or patient* or neonate* or child*or woman or women or men or man or adolescen*)
11. #9 NOT #10

12. TITLE: ((('case stud*' or 'a case of' or 'case report*' or 'in a patient' or girl or woman or man or boy or child or female or male or 'a patient of') not 'case control'))
13. #11 NOT #12

Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 3 of 4, July 2014)

Searched 29 September 2014.

Same search as for Cochrane Central Register of Controlled Trials.

EMBASE Classic + EMBASE (via Ovid) (1947 to 25 September 2014)

Searched 26 September 2014.

Search strategy

1. exp *acute kidney failure/ (25,170)
2. exp *kidney tubule necrosis/ (1745)
3. exp acute disease/ and exp *kidney disease/ (2964)
4. exp *kidney injury/ (9663)
5. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (11,879)
6. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (30,030)
7. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (4742)
8. aki.tw. (6336)
9. 'contrast induced nephropathy'.tw. (1830)
10. exp *contrast induced nephropathy/ (1310)
11. exp *reperfusion injury/ (20,312)
12. (reperfusion adj5 (injur* or isch?emi*)).tw. (53,348)
13. exp *delayed graft function/ or 'delayed graft function*'.tw. (3768)
14. ((renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. or (or/1-10)) and (11 or 12 or 13) (9795)
15. or/1-10,14 (70,674)
16. limit 15 to yr='2004 -Current' (37,141)
17. (Sera or Serum or Serologic* or urine or urinary).ti. (492,367)
18. (sample* or specimen*).tw. (1,773,754)
19. (Sera or Serum or Serologic*).tw. (1,231,104)
20. plasma.tw. (883,935)
21. blood.tw. (1,964,937)
22. (Urine or Urinary).tw. (527,090)
23. exp blood/ (2,032,361)
24. exp plasma/ (150,511)
25. exp serum/ (238,704)
26. exp urine/ (175,881)
27. (18 and (or/19-26)) or 17 (971,361)
28. exp blood analysis/ (120,308)
29. exp urinalysis/ (73,802)
30. 27 or 28 or 29 [serum blood urine sample or analysis] (1,096,197)
31. (NGAL or 'Neutrophil gelatinase-associated lipocalin' or 'lipocalin 2' or lcn2).tw. (3221)
32. exp neutrophil gelatinase associated lipocalin/ (3536)
33. (TIMP-2 or 'TIMP 2' or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2').tw. (4071)
34. exp 'tissue inhibitor of metalloproteinase 2'/ (4696)

35. exp kidney injury molecule 1/ [used for tim-1 / kim 1] (1011)
36. (KIM-1 or TIMD1 or TIM-1 or 'Hepatitis A virus cellular receptor 1').tw. (965)
37. (Cystatin C or 'Cystatin C').tw. (4931)
38. exp cystatin C/ (6100)
39. (L-FABP or (Liver adj2 'Fatty acid-binding protein')).tw. (962)
40. exp fatty acid binding protein/ (5723)
41. (IL-18 or 'IL 18' or Interleukin-18 or 'Interleukin 18').tw. (7934)
42. exp interleukin 18/ (9525)
43. (MIOX or 'myo-inositol oxygenase').tw. (75)
44. exp inositol oxygenase/ (74)
45. (NTN1 or netrin-1).tw. (717)
46. exp netrin 1/ (743)
47. (IGFBP7 or IBP-7 or 'IGF-binding protein 7' or 'Insulin-like growth factor-binding protein 7').tw. (274)
48. exp somatomedin binding protein/ [synonym for Insulin-Like Growth Factor Binding Proteins?] (5151)
49. exp potassium/ or exp potassium blood level/ (111,615)
50. potassium.tw. (144,039)
51. exp creatinine blood level/ or exp creatinine urine level/ or exp creatinine/ [11] (127,699)
52. (Creat or Crea or creatinine).tw. (116,882)
53. ('T Prot' or 'Total Protein').tw. (29,574)
54. exp protein/ [12] (408,671)
55. (Alb or Albumin).tw. (156,441)
56. exp serum albumin/ or exp albumin blood level/ or exp human albumin/ or exp albumin/ or exp human serum albumin/ (124,522)
57. exp acute phase protein/ [broader than albumin and includes more such as retinol binding protein] (7283)
58. exp urea nitrogen blood level/ (21,193)
59. (BUN or Blood Urea Nitrogen).tw. (15,003)
60. (AAP or AP-N or hAPN orAP-M or 'EC=3.4.11.2' or 'Alanine aminopeptidase').tw. (3381)
61. exp microsomal aminopeptidase/ [Alanine aminopeptidase] (4941)
62. (ALP-1 or GCAP or PLAP-like or Alkaline phosphatase or Alkaline phosphatase or placental-like).tw. (72,967)
63. exp alkaline phosphatase/ [17 emtree only] (84,260)
64. (GST or glutathione-S-transferase or 'Glutathione S-transferase A2' or 'EC=2.5.1.18').tw. [18] (32,592)
65. exp glutathione transferase/ (30,078)
66. exp gamma glutamyltransferase/ or exp gamma glutamyl transferase blood level/ [20] (22,684)
67. ('GGT 5' or GGT5 or 'gamma glutamyltransferase 5' or 'glutamyl transpeptidase').tw. (5744)
68. (('N-acetyl' adj2 glucosaminidase) or 'Bifunctional protein*' or ncoat* or NAG or OGA).tw. (6637)
69. exp acetylglucosaminidase/ [21] (2190)
70. 'glucosaminidase'.tw. (5217)
71. exp n acetylglucosaminyltransferase/ or exp n acetylglucosamine/ or exp histone acetyltransferase/ (12,481)
72. exp beta 2 microglobulin/ [22] (13,632)
73. (microglobulin or AMBP).tw. (14,268)
74. exp alpha 1 microglobulin/ [23] (1314)
75. exp retinol binding protein/ [24] (3435)
76. 'retinol binding protein 4'.tw. (800)
77. microalbumin.tw. [25] (974)
78. exp microalbuminuria/ (12,250)
79. (clusterin or 'Apo-J' or 'TRPM-2').tw. or exp clusterin/ (3246)
80. ('CYR-61' or 'CRIM-1' or 'Cysteine-rich protein' or 'Cysteine-rich motor neuron 1 protein').tw. or exp cysteine rich protein 61/ [27] (1377)
81. ('SPP-1' or Osteopontin).tw. or exp osteopontin/ (10,784)
82. (NHE3 or NHE or 'exchanger 9B2' or 'exchanger isoform').tw. or exp proton sodium exchange/ or exp sodium proton exchange protein 3/ [29] (6082)
83. 'Alpha-2-HS-glycoprotein'.tw. or exp fetuin A/ (1182)
84. Klotho.tw. or exp Klotho protein/ (1512)

85. exp calbindin 1/ or exp calbindin/ or (CALB1 or calbindin).tw. [32] (5621)
86. exp fatty acid binding protein/ or (h-FABP or MDGI or M-FABP or 'Fatty acid-binding protein').tw. [33] (7116)
87. (renin or 'ec=3.4.23.15').tw. [34] (54,978)
88. exp kidney injury/di [Diagnosis] (1567)
89. exp acute kidney failure/di [Diagnosis] (3599)
90. (biomarker* or 'bio* marker*' or marker*).tw. (770,398)
91. diagnostic*.tw. (718,123)
92. factor.tw. (1,463,890)
93. (test or tests).tw. (1,841,173)
94. exp biological marker/ (131,802)
95. or/31-94 [specific biomarkers SHs, txtwords, and biomarker general terms] (5,223,158)
96. exp biological marker/ (131,802)
97. (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif* or accura* or marker* or biomarker* or sensitivity).tw. (10,694,092)
98. 96 or 97 [detect filter] (10,708,959)
99. (exp animals/ or exp nonhuman/ or animal experiment/ or exp veterinary medicine/ or exp experimental animal/) not exp human/ (5,908,462)
100. (16 and 30 and 95 and 98) not 99 (2664)
101. 100 not (('case stud*' or 'a case of' or 'case report*' or 'in a patient' or girl or woman or man or boy or child or female or male or 'a patient of') not 'case control').ti. (2502)

International Clinical Trials Registry Platform (via the World Health Organization)

Searched 29 September 2014.

Search strategy

1. (acute kidney injury OR AKI) AND biomarker* [standard search] (282 results)
2. (acute kidney injury OR AKI OR Acute renal failure) AND (identif* OR recogni* OR diagnos* OR indicat* OR correlat* OR prognosis OR predict* OR subclinical OR detect* OR monitor* OR stratif* OR accuracy OR sensitivity) [Advanced search] (49 results)

MEDLINE (via Ovid) (1946 to week 3 September 2014)

Searched 26 September 2014.

Search strategy

1. acute kidney injury/ or kidney tubular necrosis, acute/ (34,230)
2. Acute Disease/ and exp Kidney Diseases/ (7675)
3. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (6635)
4. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (21,345)
5. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3418)
6. aki.tw. (3076)
7. 'contrast induced nephropathy'.tw. (944)
8. (reperfusion adj5 (injur* or isch?emi*)).tw. or reperfusion injury/ or reperfusion/ (46,033)
9. exp Delayed Graft Function/ or 'delayed graft function*'.tw. (2299)
10. ((renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. or (or/1-7)) and (8 or 9) (7053)

11. or/1-7,10 [AKI] (56,812)
12. limit 11 to yr='2004 -Current' (22,491)
13. (Sera or Serum or Serologic* or urine or urinary).ti. (366,534)
14. (sample* or specimen*).tw. (1,272,203)
15. exp Analytic Sample Preparation Methods/ or exp Blood Specimen Collection/ or exp Urine Specimen Collection/ or exp Specimen Handling/ or exp Specimen Handling/ (281,322)
16. (Sera or Serum or Serologic*).tw. (877,395)
17. plasma.tw. (675,552)
18. blood.tw. (1,343,744)
19. (Urine or Urinary).tw. (352,430)
20. blood/ (48,286)
21. exp plasma/ (16,374)
22. exp serum/ (61,384)
23. urine/ (33,925)
24. or/14-23 [broadest search] (3,896,894)
25. ((or/16-23) and (or/14-15)) or 13 [refined search] (702,912)
26. exp Acute Kidney Injury/bl, ur or kidney tubular necrosis, acute/bl, ur (2902)
27. (bl or ur).fs. and (10 or 9) (1624)
28. exp Urinalysis/ (4768)
29. or/25-28 [refined search OR subheading bl ur] (708,078)
30. biomarker*.tw. (87,588)
31. 'bio* marker*'.tw. (18,195)
32. exp Biological Markers/ (646,975)
33. marker*.tw. (480,182)
34. diagnostic*.tw. (479,993)
35. factor.tw. (1,110,955)
36. (test or tests).tw. (1227167)
37. exp Acute Kidney Injury/di [Diagnosis] (3604)
38. Acute-Phase Proteins/du [Diagnostic Use] (19)
39. Insulin-Like Growth Factor Binding Proteins/du (3)
40. (NGAL or 'Neutrophil gelatinase-associated lipocalin' or 'lipocalin 2' or lcn2).tw. (1694)
41. (TIMP-2 or 'TIMP 2' or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2').tw. (3387)
42. (KIM-1 or TIMD1 or TIM-1 or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1').tw. (670)
43. (Cystatin C or 'Cystatin C').tw. (3195)
44. (L-FABP or (Liver adj2 'Fatty acid-binding protein')).tw. (769)
45. (IL-18 or 'IL 18' or Interleukin-18 or 'Interleukin 18').tw. (5940)
46. (MIOX or 'myo-inositol oxygenase').tw. (61)
47. (NTN1 or netrin-1).tw. (575)
48. (IGFBP7 or IBP-7 or 'IGF-binding protein 7' or 'Insulin-like growth factor-binding protein 7').tw. (170)
49. potassium.tw. or exp Potassium/ (160,692)
50. (Creat or Crea or creatinine).tw. (75,931)
51. ('T Prot' or 'Total Protein').tw. (20,553)
52. (Alb or Albumin).tw. (109,497)
53. (BUN or Blood Urea Nitrogen).tw. (9374)
54. (AAP or AP-N or hAPN orAP-M or 'EC=3.4.11.2' or 'Alanine aminopeptidase').tw. (2431)
55. (ALP-1 or GCAP or PLAP-like or Alkaline phosphatase or Alkaline phosphatase or placental-like).tw. (52,614)
56. (GST or glutathione-S-transferase or 'Glutathione S-transferase A2' or 'EC=2.5.1.18').tw. (27,618)
57. (('N-acetyl' adj2 glucosaminidase) or 'Bifunctional protein*' or ncoat* or NAG or OGA).tw. (5209)
58. ((alpha* adj2 microglobulin) or AMBP).tw. (1206)
59. clusterin.tw. (1491)

60. ('Apo-J' or 'TRPM-2').tw. (185)
61. ('Cysteine-rich protein' or 'Cysteine-rich motor neuron 1 protein').tw. (640)
62. ('CYR-61' or 'CRIM-1').tw. (17)
63. (SPP-1 or Osteopontin).tw. (6369)
64. (NHE3 or NHE or 'exchanger 9B2' or 'exchanger isoform').tw. (2922)
65. 'Alpha-2-HS-glycoprotein'.tw. (231)
66. Klotho.tw. (832)
67. (CALB1 or calbindin).tw. (4203)
68. (h-FABP or MDGI or M-FABP or 'Fatty acid-binding protein').tw. (3785)
69. (renin or 'ec=3.4.23.15').tw. (42,939)
70. or/30-69 [additional biomarkers] (3,740,487)
71. (exp animals/ or exp Veterinary Medicine/ or exp Animal Experimentation/) not exp humans/ (4,020,113)
72. (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif* or accura* or marker* or biomarker* or sensitivity).tw. (7,855,298)
73. exp Biological Markers/ (646,975)
74. 72 or 73 [predict / diagnose filter] (8,047,219)
75. 12 and 29 and 70 and 74 [all concepts] (2309)
76. 75 not 71 [not animal studies] (1830)
77. limit 76 to case reports (159)
78. 76 not 77 [not case studies] (1671)

MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (25 September 2014)

Searched 26 September 2014.

Search strategy

1. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (1403)
2. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (1002)
3. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (144)
4. aki.tw. (741)
5. 'contrast induced nephropathy'.tw. (144)
6. ((reperfusion adj5 (injur* or isch?emi*)) or 'delayed graft function*').tw. (2530)
7. (renal or kidney* or nephr*).tw. or (or/1-5) (36,995)
8. 6 and 7 (476)
9. or/1-5,8 [AKI] (2887)
10. limit 9 to yr='2004 -Current' (2719)
11. (sample* or specimen*).tw. (139,336)
12. (Sera or Serum or Serologic*).tw. (45,535)
13. plasma.tw. (39,175)
14. blood.tw. (74,094)
15. (Urine or Urinary).tw. (18,581)
16. (or/11-15) or biomarker*.tw. [broadest search, also biomarker*.tw added] (272,537)
17. biomarker*.tw. (15,361)
18. 'bio* marker*'.tw. (1368)
19. marker*.tw. (38,812)
20. diagnostic*.tw. (39,369)
21. factor.tw. (85,140)
22. (test or tests).tw. (109,362)

23. (NGAL or 'Neutrophil gelatinase-associated lipocalin' or 'lipocalin 2' or lcn2).tw. (330)
24. (TIMP-2 or 'TIMP 2' or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2').tw. (172)
25. (KIM-1 or TIMD1 or TIM-1 or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1').tw. (115)
26. (Cystatin C or 'Cystatin C').tw. (363)
27. (L-FABP or (Liver adj2 'Fatty acid-binding protein')).tw. (53)
28. (IL-18 or 'IL 18' or Interleukin-18 or 'Interleukin 18').tw. (417)
29. (MIOX or 'myo-inositol oxygenase').tw. (4)
30. (NTN1 or netrin-1).tw. (48)
31. (IGFBP7 or IBP-7 or 'IGF-binding protein 7' or 'Insulin-like growth factor-binding protein 7').tw. (32)
32. potassium.tw. (8454)
33. (Creat or Crea or creatinine).tw. (5047)
34. ('T Prot' or 'Total Protein').tw. (1430)
35. (Alb or Albumin).tw. (6036)
36. (BUN or Blood Urea Nitrogen).tw. (818)
37. (AAP or AP-N or hAPN orAP-M or 'EC=3.4.11.2' or 'Alanine aminopeptidase').tw. (173)
38. (ALP-1 or GCAP or PLAP-like or Alkaline phosphatase or Alkaline phosphatase or placental-like).tw. (2787)
39. (GST or glutathione-S-transferase or 'Glutathione S-transferase A2' or 'EC=2.5.1.18').tw. (1498)
40. ('GGT 5' or GGT5 or ('gamma glutamyltransferase 5' or 'glutamyl transpeptidase')).tw. (205)
41. (('N-acetyl' adj2 glucosaminidase) or 'Bifunctional protein*' or ncoat* or NAG or OGA).tw. (229)
42. (microglobulin or AMBP).tw. (329)
43. ('retinol binding protein 4' or 'plasma retinol binding protein').tw. (93)
44. microalbumin.tw. (55)
45. clusterin.tw. (105)
46. ('Apo-J' or 'TRPM-2').tw. (5)
47. ('Cysteine-rich protein' or 'Cysteine-rich motor neuron 1 protein').tw. (34)
48. ('CYR-61' or 'CRIM-1').tw. (1)
49. (SPP-1 or Osteopontin).tw. (516)
50. (NHE3 or NHE or 'exchanger 9B2' or 'exchanger isoform').tw. (164)
51. 'Alpha-2-HS-glycoprotein'.tw. (10)
52. Klotho.tw. (117)
53. (CALB1 or calbindin).tw. (146)
54. (h-FABP or MDGI or M-FABP or 'Fatty acid-binding protein').tw. (301)
55. (renin or 'ec=3.4.23.15').tw. (1387)
56. or/17-55 [biomarkers] (273,001)
57. (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif* or accura* or marker* or biomarker* or sensitivity).tw. (725,049)
58. 10 and 16 and 56 and 57 (704)
59. ((rat or rats or swine or pigs or pig or mice or mouse) not (human* or patient*)).tw. (63,154)
60. (('case stud*' or 'a case of' or 'case report*' or 'in a patient' or girl or woman or man or boy or child or female or male or 'a patient of') not 'case control').ti. (57,135)
61. 58 not (59 or 60) (578)
62. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction) adj3 (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif*)).ti. (68)
63. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction) adj3 (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif*)).ti. (6)

64. (((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*') adj3 (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif*)).ti. (0)
65. (aki adj3 (discriminat* or identif* or recogni* or diagnos* or indicat* or correlat* or prognos* or predict* or subclinical or detect* or monitor* or stratif*)).ti. (6)
66. (or/62-65) not (59 or 60) (77)
67. 66 not 61 (25)
68. 61 or 67 (603)

*meta*Register of Controlled Trials (*m*RCT)

Searched 29 September 2014.

Search strategy

1. 'Acute kidney' (161)
2. 'acute renal' AND biomarker (6)
3. 'acute renal' AND detect (10)
4. 1 OR 2 OR 3

PubMed (via the US National Library of Medicine) (1946 to September 2014)

Searched 29 September 2014.

Search strategy

1. #1 (((('acute kidney[Title] OR 'acute renal'[Title] OR 'acute tubular necrosis'[Title] OR 'aki'[Title] OR 'delayed graft function'[Title] OR 'reperfusion injur*'[Title]))) (17,542)
2. #2 ((discriminat*[Title] OR identif*[Title] OR recogni*[Title] OR diagnos*[Title] OR indicat*[Title] OR correlate*[Title] OR prognot*[Title] OR predict*[Title] OR subclinical[Title] OR detect*[Title] OR monitor*[Title] OR stratif*[Title] OR accura*[Title] OR marker*[Title] OR biomarker*[Title] OR sensitivity[Title])) (1,769,745)
3. #3 ((pubstatusaheadofprint[sb] OR publisher[sb] OR pubmednotmedline[sb])) (1,826,775)
4. #4 #1 AND #2 AND #3 (111)

Science Citation Index (via Thomson Reuters' Web of Science) (2008 to present)

Searched 29 September 2014.

Same search as for Conference Proceedings Citation Index – Science.

Appendix 2 AKI-Diagnostics horizon-scanning biomarker longlist

Biomarker	Number of papers	Timescale
NGAL	241	2005–14
Cystatin C	115	2004–14
IL-18	73	2005–14
KIM-1	72	2006–14
L-FABP	39	2006–14
NAG	37	2004–14
B2M	16	2006–14
IL-6	11	2007–14
α1-microglobulin	10	2005–14
GST	8	2010–13
IGFBP-7 (Nephrocheck)	8	2013–14
FENa	7	2005–14
BNP	7	2012–14
TIMP-2 (Nephrocheck)	6	2013–14
TNF-α	6	2012–14
CRP	5	2013–14
FEUrea	5	2006–14
GGT	5	2006–13
IL-10	4	2009–14
Procalcitonin	4	2009–14
HGF	4	2008–10
MCP-1	4	2008–13
IL-8	4	2009–12
Lactate dehydrogenase	4	2013–14
AAP	3	2012–14
AP	3	2006–14
Hepcidin	3	2011–13
H-FABP	3	2013–14
hsCRP	3	2011–14
Renin	3	2013–14
SAA	3	2011–13
ADMA	3	2012–13
Angiotensinogen	3	2013
VEGF	3	2008–14
Adiponectin	2	2013–14

Biomarker	Number of papers	Timescale
α-GST	2	2013
AOPP	2	2010–12
CXCR1	2	2012–14
EPO	2	2013–14
F2-isoprostanes	2	2011–12
FB	2	2012–13
GT	2	2011–14
HDL	2	2013
LDH	2	2013–14
LVEF	2	2013
MMP-9	2	2009
Osteopontin	2	2009–10
sRAGE	2	2012–13
SUA	2	2012–13
Vitamin D	2	2012–13
vWF	2	2014
Clusterin	2	2013
EGF	2	2013
FLC	2	2013
PAI-1	2	2012
pi-GST	2	2013
Semaphorin 3A	2	2014
AGP	1	2009
ALP	1	2013
Angiopoietin-1	1	2014
Angiopoietin-2	1	2014
Apolipoprotein M	1	2014
Aprotinin	1	2008
AQP 1	1	2006
AQP 2	1	2006
ARC	1	2012
CD14	1	2009
CXCL10	1	2008
D-dimer	1	2014
Dihydroneopterin	1	2010
EA	1	2013
ELA-2	1	2014
enRAGE	1	2013
EO	1	2014

Biomarker	Number of papers	Timescale
EPC	1	2014
ESAM	1	2014
E-selectin	1	2014
esRAGE	1	2012
FEK	1	2005
FEMg	1	2005
FGF	1	2009
FGF-2	1	2013
FGF-23	1	2013
FST	1	2014
GA	1	2012
Hb	1	2013
HMGB-1	1	2013
HO-1	1	2014
Hyaluronic acid	1	2014
ICAM-1	1	2014
IL-19	1	2011
Kynurenine	1	2014
LDL	1	2013
MicroRNA-21	1	2013
MIOX	1	2014
MMP-8	1	2014
Neopterin	1	2010
Netrin-1	1	2014
NT-ProBNP	1	2014
PAPP-A	1	2013
PDGF	1	2009
PGF2alpha	1	2011
PlGF	1	2013
Plasma homocysteine	1	2005
ProANP	1	2014
Pro-ENK	1	2013
RBP	1	2013
RCG-32	1	2014
s2-microglobulin	1	2013
sCD25	1	2014
SDMA	1	2012
Serum uric acid	1	2012
TGF-β1	1	2012

Biomarker	Number of papers	Timescale
Thrombomodulin	1	2014
TIE-2	1	2014
TIMP-1	1	2013
TLR4	1	2012
Uric acid	1	2011
Urinary glutamyl	1	2014
Vancomycin trough	1	2013
VCAM-1	1	2014
α1-antitrypsin	1	2010
α1-GST	1	2010

AAP, alanine aminopeptidase; ADMA, asymmetric dimethylarginine; AGP, alpha-1-acid glycoprotein; ALP, alkaline phosphatase; AOPP, advanced oxidation protein products; AP, alkaline phosphatase; AQP, aquaporin; ARC, activity-regulated cytoskeleton-associated protein; B2M, beta-2-microglobulin; CD14, monocyte differentiation antigen CD14; CRP, C-reactive protein; CXCL10, C-X-C motif chemokine 10; CXCR1, C-X-C chemokine receptor type 1; EA, endotoxin activity; EGF, epidermal growth factor; ELA-2, neutrophil elastase-2; enRAGE, extracellular newly identified receptor for advanced glycation end products; EO, endogenous ouabain; EPC, endothelial progenitor cell; EPO, erythropoietin; ESAM, endothelial cell-selective adhesion molecule; esRAGE, endogenous secretory receptor for advanced glycation end products; FB, fluid balance; FEK, fractional excretion of potassium; FEMg, fractional excretion of magnesium; FENa, fractional excretion of sodium; FEUrea, fractional excretion of urea; FGF, fibroblast growth factor; FLC, free light chain; FST, furosemide stress test; GA, glycated albumin; GGT, gamma-glutamyl transferase; GST, glutathione-*S*-transferase; GT, glutamyl transpeptidase; Hb, haemaglobin; HDL, high-density lipoprotein; H-FABP, heart-type fatty acid-binding protein; HGF, hepatocyte growth factor; HMGB-1, high moblity group box 1; HO-1, heme oxygenase-1; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MCP-1, monocyte chemoattractant protein-1; microRNA-21, micro ribonucleic acid-21; MIOX, myo-inositol oxygenase; MMP-8, matrix metallopeptidase-8; MMP-9, matrix metallopeptidase-9; NT-ProBNP, N-terminal pro-brain natriuretic peptide; PAI-1, plasminogen activator inhibitor 1; PAPP-A, pregnancy-associated plasma protein A; PDGF, platelet-derived growth factor; PGF2alpha, prostaglandin F2-alpha; PlGF, placental growth factor; proANP, pro-atrial natriuretic peptide; pro-ENK, pro-encephalin A; RBP, retinal binding protein; *RCG-32*, response gene to complement 32; SAA, serum amyloid A; sCD25, soluble monocyte differentiation antigen CD25; SDMA, symmetric dimethylarginine; sRAGE, soluble isoform of a receptor for advanced glycation end products; SUA, serum uric acid; TGF-1, transforming growth factor-beta-1; TIE-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; TLR4, Toll-like receptor 4; VCAM-1, vascular cell adhesion molecule-1; vWF, von Willebrand factor.

Appendix 3 AKI-Diagnostics sample search strategy: search 2 – evidence for candidate tests

ClinicalTrials.gov (via the US National Institutes of Health; Advanced Search Interface)

Searched 30 November 2015.

Search strategy

1. Search Terms: NGAL OR Lipocalin OR LCN2 OR uNGAL OR sNGAL OR siderocalin OR 'oncogene 24p3' OR 'cystatin c' OR 'gamma trace' OR 'Neuroendocrine basic polypeptide' OR 'Post-gamma-globulin'
2. Search Terms: 'IL 18' OR 'Interleukin 18' OR 'Iboctadekin' OR 'Interferon gamma-inducing factor' OR 'Interleukin-1 gamma' OR KIM-1 OR TIMD1 OR TIM-1 OR 'Hepatitis A virus cellular receptor 1' OR 'kidney injury molecule 1'
3. Search Terms: L-FABP OR 'Fatty acid-binding protein 1' OR (Liver AND Fatty acid-binding protein) OR NAG OR 'Bifunctional protein' OR ncoat OR ('N-acetyl' AND glucosaminidase) OR OGA OR O-GlcNAcase OR 'Meningioma-expressed antigen 5' OR MGEA5 OR 'Hexosaminidase C'
4. Search Terms: 'Interleukin 6' OR IL-6 OR BSF-2 OR IFN-beta-2 OR 'B-cell stimulatory factor 2' OR 'CTL differentiation factor' OR 'Hybridoma growth factor' OR 'Interferon beta-2' OR BNP OR 'B-type natriuretic peptide'
5. Search Terms: nephrocheck OR 'Metalloproteinase inhibitor 2' OR 'tissue inhibitor of metalloproteinase-2' OR timp-2 OR IGFBP7 OR IBP-7 OR IGFBP-rP1 OR 'IGF-binding protein 7' OR 'MAC25 protein' OR 'PGI2-stimulating factor' OR 'Prostacyclin-stimulating factor'
6. Search Terms: 'Tumor-derived adhesion factor' OR 'Tumour-derived adhesion factor' OR 'Tissue Necrosis Factor' OR 'Tumor necrosis factor' OR 'Tumour necrosis factor' OR 'TNF-alpha' OR 'TNF-a'
7. 1 or 2 or 3 or 4 or 5 or 6
8. Conditions: Acute AND (renal OR kidney OR 'tubular necrosis')
9. 7 AND 8

Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 10 of 12, October 2015)

Searched 30 November 2015.

Search strategy

#1 MeSH descriptor: [Acute Kidney Injury] explode all trees

#2 MeSH descriptor: [Acute Disease] explode all trees

#3 MeSH descriptor: [Kidney Diseases] explode all trees

#4 #2 and #3

#5 (Acute near/3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)):ti,ab

#6 (Acute near/3 (renal disease* or renal injury or renal failure or renal dysfunction)):ti,ab

#7 ((Acute near/3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*'):ti,ab

#8 (AKI):ti,ab

#9 ('contrast induced nephropathy'):ti,ab

#10 {or #1, #4-#9}

#11 (renal or kidney* or nephr*):ti,ab

#12 #1 or #4

#13 #11 or #12

#14 (reperfusion near/5 (injur* or isch?emi*)):ti,ab

#15 MeSH descriptor: [Reperfusion Injury] explode all trees

#16 ('delayed graft function*'):ti,ab

#17 MeSH descriptor: [Delayed Graft Function] explode all trees

#18 {or #14-#17} and #13

#19 #10 or #18 Publication Year from 2004 to 2014

#20 MeSH descriptor: [Lipocalins] this term only

#21 (NGAL or uNGAL or sNGAL or 'Neutrophil gelatinase-associated lipocalin' or 'neutrophil gelatinase lipocalin' or 'lipocalin 2' or lcn2 or 'Oncogene 24p3' or siderocalin):ti,ab

#22 MeSH descriptor: [Cystatin C] this term only

#23 ('cystatin c' or 'Gamma trace' or 'Neuroendocrine basic polypeptide' or 'Post-gamma-globulin'):ti,ab

#24 MeSH descriptor: [Interleukin-18] this term only

#25 ('IL 18' or 'Interleukin 18' or 'Iboctadekin' or 'Interferon gamma-inducing factor' or 'Interleukin-1 gamma'):ti,ab

#26 (KIM-1 or TIMD1 or TIM-1 or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1'):ti,ab

#27 MeSH descriptor: [Fatty Acid-Binding Proteins] explode all trees

#28 (L-FABP or 'Fatty acid-binding protein 1' or (Liver near/2 ('Fatty acid-binding protein'))):ti,ab

#29 MeSH descriptor: [Acetylglucosaminidase] this term only

#30 (NAG or 'Bifunctional protein*' or ncoat* or (('N-acetyl') near/3 (glucosaminidase)) or OGA or O-GlcNAcase or 'Meningioma-expressed antigen 5' or MGEA5 or 'Hexosaminidase C' or 'Histone acetyltransferase'):ti,ab

#31 MeSH descriptor: [Interleukin-6] this term only

#32 ('Interleukin 6' or IL-6 or BSF-2 or IFN-beta-2 or 'B-cell stimulatory factor 2' or 'CTL differentiation factor' or 'Hybridoma growth factor' or 'Interferon beta-2'):ti,ab

#33 MeSH descriptor: [Natriuretic Peptide, Brain] this term only

#34 ('B-type natriuretic peptide*' or BNP):ti,ab

#35 MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-2] this term only

#36 (nephrocheck or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2' or timp-2 or IGFBP7 or IBP-7 or IGFBP-rP1 or 'IGF-binding protein 7' or 'MAC25 protein' or 'PGI2-stimulating factor' or 'Prostacyclin-stimulating factor' or 'Tumo*r-derived adhesion factor'):ti,ab

#37 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees

#38 ('Tissue Necrosis Factor' or 'Tumo*r necrosis factor' or 'TNF-alpha' or 'TNF-a'):ti,ab

#39 {or #20-#38}

#40 #19 and #39

#41 MeSH descriptor: [Animals] explode all trees

#42 MeSH descriptor: [Veterinary Medicine] explode all trees

#43 MeSH descriptor: [Animal Experimentation] explode all trees

#44 MeSH descriptor: [Humans] explode all trees

#45 {or #41-#43} not #44

#46 #40 not #45

Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 11 of 12, November 2015)

Searched 30 November 2015.

Same search as for Cochrane Central Register of Controlled Trials.

Database of Abstracts of Reviews of Effects (via Wiley Online Library) (Issue 2 of 4, April 2015)

Searched 30 November 2015.

Same search as for Cochrane Database of Systematic Reviews.

EMBASE Classic + EMBASE (via Ovid) (1947 to 24 November 2015)

Searched 29 November 2015.

Search strategy

1. exp *acute kidney failure/ (25,748)
2. exp *kidney tubule necrosis/ (1746)
3. exp acute disease/ and exp *kidney disease/ (2978)
4. exp *kidney injury/ (9863)
5. exp *contrast induced nephropathy/ (1397)
6. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (13,009)
7. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (30,609)
8. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (4801)
9. aki.tw. (7002)
10. 'contrast induced nephropathy'.tw. (1935)
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (65,453)
12. exp *reperfusion injury/ (20910)
13. (reperfusion adj5 (injur* or isch?emi*)).tw. (55,051)
14. exp *delayed graft function/ (526)
15. 'delayed graft function*'.tw. (3794)
16. or/13-15 (58,543)
17. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (1,017,273)
18. 1 or 2 or 3 or 4 or 5 or 17 (1,020,779)
19. 16 and 18 (9998)
20. 11 or 19 (72,803)
21. 11 or 19 [AKI] (72,803)
22. neutrophil gelatinase associated lipocalin/ (3844)
23. (NGAL or uNGAL or sNGAL).tw. (2362)
24. ('Neutrophil gelatinase-associated lipocalin' or 'neutrophil gelatinase lipocalin' or 'lipocalin 2' or lcn2).tw,tn. (2938)
25. Oncogene 24p3.tw,tn. (5)
26. siderocalin.tw,tn. (51)
27. or/22-26 [NGAL] (4430)
28. cystatin C/ (6428)
29. cystatin c.tw. (5201)
30. Gamma trace.tw. (20)
31. Neuroendocrine basic polypeptide.tw. (0)
32. Post-gamma-globulin.tw. (7)
33. or/30-34 [Cystatin C] (6843)
34. interleukin 18/ (9916)
35. IL 18.tw. (7741)
36. Interleukin 18.tw. (2711)
37. Iboctadekin.tw. (3)
38. Interferon gamma-inducing factor.tw. (28)
39. Interleukin-1 gamma.tw. (2)
40. or/38-43 [IL-18] (12,384)
41. kidney injury molecule 1/ (1117)
42. (KIM-1 or TIMD1 or TIM-1).tw. (1045)
43. Hepatitis A virus cellular receptor 1.tw. (20)
44. kidney injury molecule 1.tw. (653)
45. 'T-cell immunoglobulin and mucin domain-containing protein 1'.tw. (0)
46. 'T-cell immunoglobulin mucin receptor 1'.tw. (0)

47. 'T-cell membrane protein 1'.tw. (0)
48. or/47-53 [KIM-1] (1689)
49. fatty acid binding protein/ (5893)
50. L-FABP.tw. (662)
51. Fatty acid-binding protein 1.tw. (42)
52. (Liver adj2 'Fatty acid-binding protein').tw. (782)
53. or/58-61 [L-FABP] (6065)
54. n acetyl beta glucosaminidase/ (4605)
55. Bifunctional protein*.tw. (836)
56. ncoat*.tw. (8)
57. NAG.tw. (4070)
58. ('N-acetyl' adj3 glucosaminidase).tw. (4830)
59. OGA.tw. (365)
60. O-GlcNAcase.tw. (408)
61. Meningioma-expressed antigen 5.tw. (2)
62. MGEA5.tw. (34)
63. Hexosaminidase C.tw. (24)
64. 'EC=3.2.1.169'.tw. (0)
65. 'EC=2.3.1.48'.tw. (0)
66. Histone acetyltransferase.tw. (2444)
67. or/65-77 [NAG] (12,925)
68. interleukin 6/ (136,429)
69. Interleukin 6.tw. (40,597)
70. IL-6.tw. (94,548)
71. BSF-2.tw. (102)
72. IFN-beta-2.tw. (21)
73. B-cell stimulatory factor 2.tw. (86)
74. CTL differentiation factor.tw. (4)
75. Hybridoma growth factor.tw. (55)
76. Interferon beta-2.tw. (30)
77. or/81-89 [IL-6] (149,048)
78. brain natriuretic peptide/ (17,988)
79. B-type natriuretic peptide*.tw. (6572)
80. BNP.tw. (13,985)
81. or/93-95 [BNP] (24,772)
82. nephrocheck.tw. (2)
83. 'tissue inhibitor of metalloproteinase 2'/ (4826)
84. Metalloproteinase inhibitor 2.tw. (15)
85. tissue inhibitor of metalloproteinase-2.tw. (609)
86. TIMP 2.tw. (3952)
87. somatomedin binding protein/ (5232)
88. (IGFBP7 or IBP-7 or IGFBP-rP1).tw. (330)
89. IGF-binding protein 7.tw. (12)
90. Insulin-like growth factor-binding protein 7.tw. (146)
91. MAC25 protein.tw. (5)
92. PGI2-stimulating factor.tw. (8)
93. Prostacyclin-stimulating factor.tw. (30)
94. or/99-110 [Nephrocheck TIMP-2 IGFBP7] (11,601)
95. tumor necrosis factor alpha/ (159,697)
96. Tissue Necrosis Factor.tw. (150)
97. Tumo?r necrosis factor.tw. (116,825)
98. TNF-alpha.tw. (103,358)
99. TNF-a.tw. (5983)

100. Tumour necrosis factor.tw. (19,564)
101. or/116-121 [TNF-a] (227,621)
102. 27 or 35 or 44 or 54 or 62 or 78 or 90 or 96 or 111 or 122 (374,119)
103. 21 and 125 (5514)
104. limit 126 to yr=‘2004 -Current’ (4843)
105. (exp animals/ or exp nonhuman/ or animal experiment/ or exp veterinary medicine/ or exp experimental animal/) not exp human/ (5,985,269)
106. 127 not 131 (3236)

Health Technology Assessment database (via Wiley Online Library) (Issue 4 of 4, October 2015)

Searched 30 November 2015.

Same search as for Cochrane Database of Systematic Reviews.

Health Management Information Consortium (HMIC) (1983 to November 2015)

Searched 30 November 2015.

Same search as for MEDLINE In-Process & Other Non-Indexed Citations (via Ovid).

International Clinical Trials Registry Platform (via the World Health Organization, Advanced Search)

Searched 30 November 2015.

Search strategy

1. Title: NGAL OR Lipocalin OR LCN2 OR uNGAL OR sNGAL OR siderocalin OR ‘oncogene 24p3’ OR ‘cystatin c’ OR ‘gamma trace’ OR ‘Neuroendocrine basic polypeptide’ OR ‘Post-gamma-globulin’
2. Title: ‘IL 18’ OR ‘Interleukin 18’ OR ‘Iboctadekin’ OR ‘Interferon gamma-inducing factor’ OR ‘Interleukin-1 gamma’ OR KIM-1 OR TIMD1 OR TIM-1 OR ‘Hepatitis A virus cellular receptor 1’ OR ‘kidney injury molecule 1’
3. Title: L-FABP OR ‘Fatty acid-binding protein’ OR NAG OR ‘Bifunctional protein’ OR ncoat OR (‘N-acetyl’ AND glucosaminidase) OR O-GlcNAcase OR ‘Meningioma-expressed antigen 5’ OR MGEA5 OR ‘Hexosaminidase C’
4. Title: ‘Interleukin 6’ OR IL-6 OR BSF-2 OR IFN-beta-2 OR ‘B-cell stimulatory factor 2’ OR ‘CTL differentiation factor’ OR ‘Hybridoma growth factor’ OR ‘Interferon beta-2’ OR BNP OR ‘B-type natriuretic peptide’
5. Title: nephrocheck OR ‘Metalloproteinase inhibitor 2’ OR ‘tissue inhibitor of metalloproteinase-2’ OR timp-2 OR IGFBP7 OR IBP-7 OR IGFBP-rP1 OR ‘IGF-binding protein 7’ OR ‘MAC25 protein’ OR ‘PGI2-stimulating factor’ OR ‘Prostacyclin-stimulating factor’
6. Title: ‘Tumor-derived adhesion factor’ OR ‘Tumour-derived adhesion factor’ OR ‘Tissue Necrosis Factor’ OR ‘Tumor necrosis factor’ OR ‘Tumour necrosis factor’ OR ‘TNF-alpha’ OR ‘TNF-a’
7. 1 or 2 or 3 or 4 or 5 or 6
8. Condition: acute kidney OR acute renal OR acute tubular necrosis OR AKI
9. 7 and 8

MEDLINE (via Ovid) (1946 to November Week 2 2015)

Searched 29 November 2015.

Search strategy

1. Acute Disease/ and exp Kidney Diseases/ (7632)
2. acute kidney injury/ (32,719)
3. kidney tubular necrosis, acute/ (2173)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (6843)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (21,178)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3393)
7. aki.tw. (3147)
8. 'contrast induced nephropathy'.tw. (971)
9. or/1-8 (51,426)
10. reperfusion injury/ (20,176)
11. reperfusion/ (4154)
12. exp Delayed Graft Function/ (663)
13. 'delayed graft function*'.tw. (2118)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (39,781)
15. or/10-14 (48,027)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (689,988)
17. 1 or 2 or 3 or 16 (697,761)
18. 15 and 17 (7094)
19. 9 or 18 [AKI] (56,709)
20. Lipocalins/ (2456)
21. (NGAL or uNGAL or sNGAL).tw. (1018)
22. ('Neutrophil gelatinase-associated lipocalin' or 'neutrophil gelatinase lipocalin' or 'lipocalin 2' or lcn2).tw,nm. (1885)
23. Oncogene 24p3.tw,nm. (4)
24. siderocalin.tw,nm. (42)
25. or/20-24 [NGAL] (2982)
26. Cystatin C/ (2620)
27. cystatin c.tw,nm. (3499)
28. Gamma trace.tw,nm. (56)
29. Neuroendocrine basic polypeptide.tw,nm. (0)
30. Post-gamma-globulin.tw,nm. (11)
31. or/26-30 [Cystatin C] (3531)
32. Interleukin-18/ (3995)
33. IL 18.tw,nm. (5449)
34. Interleukin 18.tw,nm. (4423)
35. Iboctadekin.tw,nm. (0)
36. Interferon gamma-inducing factor.tw,nm. (72)
37. Interleukin-1 gamma.tw,nm. (6)
38. or/32-37 [IL 18] (6372)
39. Hepatitis A virus cellular receptor 1.tw,nm. (19)
40. (KIM-1 or TIMD1 or TIM-1).tw,nm. (539)
41. kidney injury molecule 1.tw,nm. (381)
42. 'T-cell immunoglobulin and mucin domain-containing protein 1'.tw,nm. (0)
43. 'T-cell immunoglobulin mucin receptor 1'.tw,nm. (0)
44. 'T-cell membrane protein 1'.tw,nm. (0)
45. or/39-44 [KIM-1] (700)
46. fatty acid-binding proteins/ or myelin p2 protein/ (4046)

47. L-FABP.tw. (499)
48. Fatty acid-binding protein 1.tw,nm. (30)
49. (Liver adj2 'Fatty acid-binding protein').tw,nm. (621)
50. or/46-49 [L-FABP] (4232)
51. Acetylglucosaminidase/ (4857)
52. Bifunctional protein*.tw,nm. (770)
53. ncoat*.tw,nm. (7)
54. NAG.tw. (2998)
55. ('N-acetyl' adj3 glucosaminidase).tw,nm. (4250)
56. OGA.tw. (194)
57. O-GlcNAcase.tw,nm. (242)
58. Meningioma-expressed antigen 5.tw,nm. (1)
59. MGEA5.tw. (21)
60. Hexosaminidase C.tw,nm. (163)
61. 'EC=3.2.1.169'.tw,nm. (0)
62. 'EC=2.3.1.48'.tw,nm. (0)
63. Histone acetyltransferase.tw,nm. (2068)
64. or/51-63 [NAG] (11,007)
65. Interleukin-6/ (46701)
66. Interleukin 6.tw,nm. (57,499)
67. IL-6.tw. (63,124)
68. BSF-2.tw. (101)
69. IFN-beta-2.tw,nm. (103)
70. B-cell stimulatory factor 2.tw,nm. (82)
71. CTL differentiation factor.tw,nm. (5)
72. Hybridoma growth factor.tw,nm. (55)
73. Interferon beta-2.tw,nm. (80)
74. or/65-73 [IL-6] (82,477)
75. Natriuretic Peptide, Brain/ (10,025)
76. B-type natriuretic peptide*.tw,nm. (4073)
77. BNP.tw. (6475)
78. or/75-77 [BNP] (12,102)
79. nephrocheck.tw,nm. (0)
80. Metalloproteinase inhibitor 2.tw,nm. (8)
81. 'Tissue Inhibitor of Metalloproteinase-2'/ (2890)
82. tissue inhibitor of metalloproteinase-2.tw,nm. (3043)
83. TIMP 2.tw. (3181)
84. (IGFBP7 or IBP-7 or IGFBP-rP1).tw. (208)
85. IGF-binding protein 7.tw,nm. (10)
86. Insulin-like growth factor-binding protein 7.tw,nm. (84)
87. MAC25 protein.tw,nm. (5)
88. PGI2-stimulating factor.tw,nm. (6)
89. Prostacyclin-stimulating factor.tw,nm. (28)
90. Tumor-derived adhesion factor.tw,nm. (14)
91. or/79-90 [Nephrocheck TIMP 2 IGFBP7] (4440)
92. Tumor Necrosis Factor-alpha/ (97,576)
93. Tissue Necrosis Factor.tw,nm. (115)
94. 'Tumor necrosis factor'.tw,nm. (136,471)
95. TNF-alpha.tw. (79,914)
96. TNF-a.tw. (1226)
97. or/92-96 [TNF-a] (156,262)
98. 25 or 31 or 38 or 45 or 50 or 64 or 74 or 78 or 91 or 97 [10 Selected Biomarkers] (242,639)
99. 19 and 98 (2776)

100. limit 99 to yr='2004 -Current' (2219)
101. (exp animals/ or exp Veterinary Medicine/ or exp Animal Experimentation/) not exp humans/ (3,990,735)
102. 100 not 101 [10 Biomarkers and AKI, 2004+, not animals studies] (1383)

MEDLINE In-Process & Other Non-Indexed Citations (via Ovid) (24 November 2015)

Searched 29 November 2015.

Search strategy

1. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (1612)
2. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (1032)
3. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (150)
4. aki.tw. (872)
5. 'contrast induced nephropathy'.tw. (147)
6. or/1-5 (2805)
7. 'delayed graft function*'.tw. (169)
8. (reperfusion adj5 (injur* or isch?emi*)).tw. (2578)
9. 7 or 8 (2733)
10. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (39,482)
11. 9 and 10 (526)
12. 6 or 11 [AKI] (3193)
13. (NGAL or uNGAL or sNGAL).tw. (235)
14. ('Neutrophil gelatinase-associated lipocalin' or 'neutrophil gelatinase lipocalin' or 'lipocalin 2' or lcn2).tw,nm. (312)
15. Oncogene 24p3.tw,nm. (0)
16. siderocalin.tw,nm. (2)
17. or/13-16 [NGAL] (351)
18. cystatin c.tw,nm. (397)
19. Gamma trace.tw,nm. (0)
20. Neuroendocrine basic polypeptide.tw,nm. (0)
21. Post-gamma-globulin.tw,nm. (0)
22. or/18-21 [Cystatin C] (397)
23. IL 18.tw,nm. (419)
24. Interleukin 18.tw,nm. (134)
25. Iboctadekin.tw,nm. (0)
26. Interferon gamma-inducing factor.tw,nm. (1)
27. Interleukin-1 gamma.tw,nm. (0)
28. or/23-27 [IL-18] (455)
29. Hepatitis A virus cellular receptor 1.tw,nm. (0)
30. (KIM-1 or TIMD1 or TIM-1).tw,nm. (95)
31. kidney injury molecule 1.tw,nm. (73)
32. 'T-cell immunoglobulin and mucin domain-containing protein 1'.tw,nm. (0)
33. 'T-cell immunoglobulin mucin receptor 1'.tw,nm. (0)
34. 'T-cell membrane protein 1'.tw,nm. (0)
35. or/29-34 [KIM-1] (122)
36. L-FABP.tw. (39)
37. Fatty acid-binding protein 1.tw,nm. (2)
38. (Liver adj2 'Fatty acid-binding protein').tw,nm. (41)
39. or/36-38 [L-FABP] (59)
40. Bifunctional protein*.tw,nm. (19)

41. ncoat*.tw,nm. (0)
42. NAG.tw. (171)
43. ('N-acetyl' adj3 glucosaminidase).tw,nm. (133)
44. OGA.tw. (25)
45. O-GlcNAcase.tw,nm. (25)
46. Meningioma-expressed antigen 5.tw,nm. (0)
47. MGEA5.tw. (1)
48. Hexosaminidase C.tw,nm. (0)
49. 'EC=3.2.1.169'.tw,nm. (0)
50. 'EC=2.3.1.48'.tw,nm. (0)
51. Histone acetyltransferase.tw,nm. (132)
52. or/40-51 [NAG] (417)
53. Interleukin 6.tw,nm. (2351)
54. IL-6.tw. (5580)
55. BSF-2.tw. (0)
56. IFN-beta-2.tw,nm. (1)
57. B-cell stimulatory factor 2.tw,nm. (1)
58. CTL differentiation factor.tw,nm. (0)
59. Hybridoma growth factor.tw,nm. (1)
60. Interferon beta-2.tw,nm. (1)
61. or/53-60 [IL-6] (6473)
62. B-type natriuretic peptide*.tw,nm. (433)
63. BNP.tw. (572)
64. or/62-63 [BNP] (800)
65. nephrocheck.tw,nm. (0)
66. Metalloproteinase inhibitor 2.tw,nm. (2)
67. tissue inhibitor of metalloproteinase-2.tw,nm. (24)
68. TIMP 2.tw. (168)
69. (IGFBP7 or IBP-7 or IGFBP-rP1).tw. (29)
70. IGF-binding protein 7.tw,nm. (1)
71. Insulin-like growth factor-binding protein 7.tw,nm. (14)
72. MAC25 protein.tw,nm. (0)
73. PGI2-stimulating factor.tw,nm. (0)
74. Prostacyclin-stimulating factor.tw,nm. (0)
75. Tumo?r-derived adhesion factor.tw,nm. (1)
76. or/65-75 [Nephrocheck TIMP-2 IGFBP7] (206)
77. Tissue Necrosis Factor.tw,nm. (15)
78. 'Tumo?r necrosis factor'.tw,nm. (5964)
79. TNF-alpha.tw. (6211)
80. TNF-a.tw. (108)
81. or/77-80 [TNF-a] (9432)
82. 17 or 22 or 28 or 35 or 39 or 52 or 61 or 64 or 76 or 81 [10 biomarkers] (15,155)
83. 12 and 82 [AKI and Biomarkers] (319)
84. ((rat or rats or swine or pigs or pig or mice or mouse) not (human* or patient*)).tw. (66,543)
85. 83 not 84 (230)
86. limit 85 to yr='2004 -Current' [10 biomarkes and AKI, 2004+, not animals] (227)

NHS Economic Evaluation Database (via Wiley Online Library) (Issue 2 of 4, April 2015)

Searched 30 November 2015.

Same search as for Cochrane Database of Systematic Reviews.

PubMed (via the US National Library of Medicine) (1946 to November 2015)

Searched 30 November 2015.

Search strategy

#1 Search ('acute kidney'[Title] OR 'acute renal'[Title] OR 'acute tubular necrosis'[Title] OR 'aki'[Title] OR 'delayed graft function'[Title] OR 'reperfusion injur*'[Title]) 18,005

#2 Search (((((NGAL[Title] OR Lipocalin[Title] OR LCN2[Title] OR uNGAL[Title] OR sNGAL[Title] OR siderocalin [Title] OR 'oncogene 24p3'[Title] OR 'cystatin c'[Title] OR 'gamma trace'[Title] OR 'Neuroendocrine basic polypeptide'[Title] OR 'Post-gamma-globulin'[Title] OR 'IL 18'[Title] OR 'Interleukin 18'[Title] OR 'Iboctadekin'[Title] OR 'Interferon gamma-inducing factor'[Title] OR 'Interleukin-1 gamma'[Title] OR KIM-1 [Title] OR TIMD1[Title] OR TIM-1[Title] OR 'Hepatitis A virus cellular receptor 1'[Title] OR 'kidney injury molecule 1'[Title])) OR (L-FABP[Title] OR 'Fatty acid-binding protein 1'[Title] OR (Liver[Title] AND Fatty acid-binding protein)[Title] OR NAG[Title] OR 'Bifunctional protein'[Title] OR ncoat[Title] OR ('N-acetyl'[Title] AND glucosaminidase)[Title] OR OGA[Title] OR O-GlcNAcase[Title] OR 'Meningioma-expressed antigen 5'[Title] OR MGEA5[Title] OR 'Hexosaminidase C'[Title])) OR ('Interleukin 6'[Title] OR IL-6[Title] OR BSF-2 [Title] OR IFN-beta-2[Title] OR 'B-cell stimulatory factor 2'[Title] OR 'CTL differentiation factor'[Title] OR 'Hybridoma growth factor'[Title] OR 'Interferon beta-2'[Title] OR BNP[Title] OR 'B-type natriuretic peptide'[Title])) OR (nephrocheck[Title] OR 'Metalloproteinase inhibitor 2'[Title] OR 'tissue inhibitor of metalloproteinase-2'[Title] OR timp-2[Title] OR IGFBP7[Title] OR IBP-7[Title] OR IGFBP-rP1[Title] OR 'IGF-binding protein 7'[Title] OR 'MAC25 protein'[Title] OR 'PGI2-stimulating factor'[Title] OR 'Prostacyclin-stimulating factor'[Title])) OR ('Tumor-derived adhesion factor'[Title] OR 'Tumour-derived adhesion factor'[Title] OR 'Tissue Necrosis Factor'[Title] OR 'Tumor necrosis factor'[Title] OR 'Tumour necrosis factor'[Title] OR 'TNF-alpha'[Title] OR 'TNF-a'[Title]) 59,070

#3 Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 1,881,815

#4 Search (#1 and #2 and #4) 45

Science Citation Index (via Thomson Reuters' Web of Science) (1900 to November 2015)

Searched 30 November 2015.

Search strategy

#1 TS=('acute kidney injury' or AKI) OR TS=((Acute NEAR/3 ('kidney disease*' or 'kidney injury' or 'kidney failure' or 'kidney dysfunction'))) OR TS=((Acute NEAR/3 ('renal disease*' or 'renal injury' or 'renal failure' or 'renal dysfunction'))) OR TS=(((Acute NEAR/3 ('Tubular Necrosis' or nephrotoxic*)) or 'nephrotoxic injur*')) OR TS=('contrast induced nephropath*') OR TS=((reperfusion NEAR/5 (injur* or isch?emi*)) AND (renal or kidney* or nephr*)) OR TS=(('Delayed Graft Function') AND (renal or kidney* or nephr*))

#2 TS=(NGAL or uNGAL or sNGAL or 'Oncogene 24p3' or siderocalin or 'Neutrophil gelatinase-associated lipocalin' or 'neutrophil gelatinase lipocalin' or 'lipocalin 2' or lcn2)

#3 TOPIC: ('cystatin c' or 'Gamma trace' or 'Neuroendocrine basic polypeptide' or 'Post-gamma-globulin')

#4 TOPIC: ('IL 18' or 'Interleukin 18' or 'Iboctadekin' or 'Interferon gamma-inducing factor' or 'Interleukin-1 gamma')

#5 TOPIC: (KIM-1 or TIMD1 or TIM-1 or 'Hepatitis A virus cellular receptor 1' or 'kidney injury molecule 1')

#6 TOPIC: (L-FABP or 'Fatty acid-binding protein 1' or ((Liver near/2 ('Fatty acid-binding protein'))))

#7 TOPIC: (NAG or 'Bifunctional protein*' or ncoat* or (('N-acetyl') near/3 (glucosaminidase)) or OGA or O-GlcNAcase or 'Meningioma-expressed antigen 5' or MGEA5 or 'Hexosaminidase C' or 'Histone acetyltransferase')

#8 TOPIC: ('Interleukin 6' or IL-6 or BSF-2 or IFN-beta-2 or 'B-cell stimulatory factor 2' or 'CTL differentiation factor' or 'Hybridoma growth factor' or 'Interferon beta-2')

#9 TOPIC: ('B-type natriuretic peptide*' or BNP)

#10 TS=(nephrocheck or 'Metalloproteinase inhibitor 2' or 'tissue inhibitor of metalloproteinase-2' or timp-2 or IGFBP7 or IBP-7 or IGFBP-rP1 or 'IGF-binding protein 7' or 'MAC25 protein' or 'PGI2-stimulating factor' or 'Prostacyclin-stimulating factor' or 'Tumo#r-derived adhesion factor')

#11 TOPIC: ('Tissue Necrosis Factor' or 'Tumo#r necrosis factor' or 'TNF-alpha' or 'TNF-a')

#12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2

#13 #12 AND #1

#14 TS= (mice or mouse or rat or rats or hamster* or sheep or animal* or rabbit* or dog or dogs or cat or cats or chicken* or poultry or pig or pigs or swine or swines or horse or horses or cow or cows or bovine*) NOT TS=(human* or patient* or neonate* or child*or woman or women or men or man or adolescen*)

#15 TI= (mice or mouse or rat or rats or hamster* or sheep or animal* or rabbit* or dog or dogs or cat or cats or chicken* or poultry or pig or pigs or swine or swines or horse or horses or cow or cows or bovine*)

#16 #15 OR #14

#17 #13 not #16

Conference Proceedings Citation Index – Science (via Thomson Reuters' Web of Science) (1990 to November 2015)

Searched 30 November 2015.

Same as search for Science Citation Index.

Appendix 4 AKI-Diagnostics systematic review data extraction proforma

Ref ID:		Reviewer initials:		Data entered:
Citation				
Authors:				
Title:				
Journal:		Year:		Pages:
		Vol:		
Study				
Design:[a]		Aim:		
Location:[b]				
Funding:	Industry	Charity	Conflict of interest declared:	Yes
	Government	Other		No
	Research council	Not reported		
Reporting standard:	REMARK	STARD	Other (detail)	
	STROBE	TRIPOD	Not reported	
Population				
Setting:	Critical care unit	Single site	Area evaluated:	Clinical validity/ utility
	Emergency dept.	Multisite[d]		Analytical validity
	Cardiac surgery	*n*		Cost-effectiveness
	Laboratory[c]			Other (specify)
	Other (specify)			
Study duration (months):			Inclusion criteria:	
Recruitment period:				
Recruitment method (consecutive, random, matched, retro or prospective, matched, etc.):			Exclusion criteria:	
Details of study throughput:	CONSORT diagram	Sample size/power calculation reported:	Yes	
	Written statement		No	
	Other (detail)			
	Not reported			

a Complete page 6 if trial design.
b Country (or countries) of study.
c Studies of analytical validity only.
d Include laboratories only if entirely laboratory-based.

APPENDIX 4

Characteristics	Group 1	Group 2	Group 3
Patient group (detail)			
Total number			
Number (%) with previous AKI			
Age range			
Mean (SD)			
Median (IQR)			
Number male (%)			
Number female (%)			
Ethnicity (%)			
White			
Asian			
Black			
Other			
Comorbidities			
Relevant lifestyle factors			

Between group difference at baseline:	Yes	Baseline difference adjusted:	Yes	Follow-up duration:
	No		No	
	Unclear		Unclear	Median follow-up:

Record any key differences in the *Notes* section on page 5.

Biomarker details

Features	Biomarker 1	Biomarker 2	Biomarker 3	Reference method or comparator test
Name of analyte				
Test name				
Manufacturer				
Sample matrix used [e.g. urine, serum, plasma (incl. type)]				
Collection timing and frequency (e.g. on admission, every 2 hours)				
Test platform/method used				
Test purpose (e.g. diagnosis, prognosis, risk prediction)				
Cut-off threshold applied				
Prespecified threshold (e.g. reported in methods)	Y/N	Y/N	Y/N	Y/N
Method to determine cut-off (e.g. level recommended for assay)				
Time between index and reference tests				
Assessor blind to reference test results	Y/N	Y/N	Y/N	Y/N
Number of samples per patient				
Number of laboratoriess used				
Test timing to AKI diagnosis				

If *reference method*, enter name of classification system only. If comparator biomarker, enter relevant details.

Main findings				
Study endpoints:				
Patient outcomes[a]	**Biomarker 1[b]**	**Biomarker 2[b]**	**Biomarker 3[b]**	**Reference method/ comparator[b]**
Patient group (detail)				
Baseline kidney function				
Classification system used: (RIFLE, AKIN, KDIGO or details if other method used)				
Number (%) diagnosed with AKI				
Cause(s) of AKI [e.g. cardiac surgery (specify if on- or off-pump), low blood pressure, etc.]				
Number (%) patients at (from classification above):				
1				
2				
3				
Other (as above)				
Number (%) of patients with:				
Recovery of kidney function				
Chronic kidney disease				
Renal replacement therapy				
Re-admission				
Death				
Average length of stay				
Related costing data (incl. cost of biomarker, laboratory costs, staff time, QALY data, etc.). If unsure, add page reference				

a If individual results given for adults and children, report these separately.
b Replace with relevant biomarker name.

Test validity	Biomarker 1[a]	Biomarker 2[a]	Biomarker 3[a]	Reference method/ comparator[a]
Total number of tests				
Test failure rate				
Distribution of analyte (across the population):				
Mean				
SD				
CV%				
Range				
Median				
Interquartile range				

APPENDIX 4

Test validity							Biomarker 1[a]	Biomarker 2[a]	Biomarker 3[a]	Reference method/ comparator[a]
True positive (TP), false positive, true negative (TN), false negative (FN) vs. gold standard (or comparator)										
	GS +	GS –	GS +	GS –	GS +	GS –	*Include only if table presented*			
Test +	TP	FP	TP	FP	TP	FP				
Test –	FN	TN	FN	TN	FN	TN				

Test validity	Biomarker 1[a]	Biomarker 2[a]	Biomarker 3[a]	Reference method/ comparator[a]
Sensitivity, 95% CI[b]				
Specificity, 95% CI[b]				
Likelihood ratios, 95% CI[b]				
ROC curve present	Y/N	Y/N	Y/N	Y/N
AUC and 95% CI[b]				
Univariate analysis:				
Odds/hazard ratios, 95% CI[b]				
Dichotomised or continuous	D/C	D/C	D/C	D/C
Multivariate analysis:				
Odds/hazard ratios, 95% CI[b]				
Dichotomised or continuous	D/C	D/C	D/C	D/C
Variables adjusted for (detail)				

CV%, coefficient of variation; ROC, receiver operating characteristic.
a Replace with relevant biomarker name.
b Document if confidence intervals are not provided.

Brief summary of key findings	Notes (incl. key limitation of study)

Appendix 5 QUADAS-2 assessment

Phase 1: state the review question

Patients (setting, intended use of index test, presentation, prior testing):	ICU/ED/cardiac surgery; adult and child populations; diagnosis or prognosis of acute kidney injury
Index test(s):	Nephrocheck; NGAL; cystatin C
Reference standard and target condition:	AKI diagnosed on the basis of creatinine/urine output criteria → classification systems: KDIGO, AKIN, RIFLE

Phase 2: draw a flow diagram for the primary study

Phase 3: risk of bias and applicability judgments

QUADAS-2 is structured so that four key domains are each rated in terms of the risk of bias and the concern regarding applicability to the research question (as defined above). Each key domain has a set of signalling questions to help reach the judgments regarding bias and applicability.

Domain 1: patient selection

A. Risk of bias

Describe methods of patient selection:

- Was a consecutive or random sample of patients enrolled? Yes/no/unclear
- Was a case–control design avoided? Yes/no/unclear
- Did the study avoid inappropriate exclusions? Yes/no/unclear

Could the selection of patients have introduced bias? Risk: low/high/unclear

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

Is there concern that the included patients do not match the review question? Concern: low/high/unclear

Domain 2: index test(s)

If more than one index test was used, please complete for each test.

A. Risk of bias

Describe the index test and how it was conducted and interpreted:

- Were the index test results interpreted without knowledge of the results of the reference standard? Yes/no/unclear
- If a threshold applicability was used, was it prespecified? Yes/no/unclear

Could the conduct or interpretation of the index test have introduced bias? Risk: low/high/unclear

B. Concerns regarding applicability

Is there concern that the index test, its conduct or interpretation differ from the review question? Concern: low/high/unclear

Domain 3: reference standard

A. Risk of bias

Describe the reference standard and how it was conducted and interpreted:

- Is the reference standard likely to correctly classify the target condition? Yes/no/unclear
- Were the reference standard results interpreted without knowledge of the results of the index test? Yes/no/unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? Risk: low/high/unclear

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question? Concern: low/high/unclear

Domain 4: flow and timing

A. Risk of bias

Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram):

Describe the time interval and any interventions between the index test(s) and the reference standard:

- Was there an appropriate interval between the index test(s) and the reference standard? Yes/no/unclear
- Did all patients receive a reference standard? Yes/no/unclear
- Did patients receive the same reference standard? Yes/no/unclear
- Were all patients included in the analysis? Yes/no/unclear

Could the patient flow have introduced bias? Risk: low/high/unclear

Appendix 6 Characteristics of eligible studies

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
524	Adademir 2012[73]	Turkey	Clinical	Cardiac (single)	Adults	Other	NGAL (urine)	55	N/N
983	Aghel 2010[74]	USA, Belgium	Clinical	Unclear (single)	Adults	Other	NGAL (serum)	91	Y/Y
1390	Åhlström 2004[75]	Finland	Clinical	Critical care (single)	Adults	ADQI Group consensus	Cystatin C (serum)	202	N/N
7818	Al-Beladi 2014[76]	Saudi Arabia	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (serum)	84	N/N
117	Alcaraz 2014[77]	Spain	Clinical/analytical	Critical care (single)	Children	RIFLE	NGAL (urine)	106	Y/Y
125	Alharazy 2014[78]	Malaysia	Clinical/analytical	Cardiac: contrast (single)	Adults	Other	NGAL (serum)	100	Y/Y
122	Arthur 2014[79]	USA	Clinical	Cardiac (multisite, $n = 4$)	Adults	AKIN	Cystatin C (urine)/ NGAL (urine)	105	N/N
149	Ataei 2014[80]	Iran	Clinical/analytical	Critical care (single)	Children	RIFLE	Cystatin C (serum)	107	Y/Y
349	Aydogdu 2013[32]	Turkey	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (plasma, urine)/NGAL (plasma, urine)	151	Y/Y
982	Bagshaw 2010[81]	Australia	Clinical	Critical care (multisite, $n = 2$)	Adults	RIFLE	NGAL (plasma, urine)	83	Y/Y
5501	Bargnoux 2013[82]	France	Analytical	Laboratory (multisite, $n = 2$)	Not specified	–	NGAL (urine)	100	N/N
20	Basu 2014[83]	USA	Clinical	Critical care (multisite, $n = 17$)	Children	KDIGO	NGAL (plasma)	214	Y/Y
1030	Bell 2009[84]	Sweden	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (serum)	271	N/N
11252	Bell 2015[85]	Sweden	Clinical	Critical care (single)	Adults	KDIGO	Nephrocheck (urine)/ NGAL (urine)/cystatin C (urine)	94	N/N
1170	Bennett 2008[86]	USA	Clinical/analytical	Cardiac (single)	Children	Other	NGAL (urine)	196	Y/Y
82	Bihorac 2014[33]	USA	Clinical	Critical care (multisite, $n = 23$)	Adults	KDIGO	Nephrocheck (urine)	408	Y/Y
112	Bojan 2014[87]	France	Clinical	Cardiac (single)	Children	AKIN	NGAL (urine)	200	Y/Y

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
11386	Bojic 2015[88]	Serbia	Clinical	Critical care (single)	Adults	KDIGO	NGAL (serum, urine)	103	N/N
532	Breidthardt 2012[89]	Switzerland	Clinical	Emergency department (multisite, $n = 3$)	Adults	AKIN	NGAL (plasma)	207	Y/Y
926	Briguori 2010[90]	Italy	Clinical	Cardiac: contrast (single)	Adults	AKIN	Cystatin C (serum)	410	Y/Y
826	Cai 2010[91]	Sweden	Analytical	Laboratory (single)	Not specified	–	NGAL (urine)	38	N/N
450	Cantinotti 2012[92]	Italy	Clinical	Cardiac (single)	Children	RIFLE	NGAL (urine)	135	Y/Y
52	Cemil 2014[93]	Turkey	Clinical	Emergency department (single)	Adults	Not reported	NGAL (serum)	60	Y/Y
597	Chen 2012[34]	Taiwan	Clinical	Critical care (single)	Adults	AKIN	Cystatin C (serum, urine)/NGAL (serum, urine)	150	Y/Y
390	Cho 2013[35]	South Korea	Clinical	Critical care (single)	Adults	AKIN	NGAL (urine)	145	Y/Y
23	Cho 2014[94]	South Korea	Clinical	Critical care (single)	Adults	RIFLE	NGAL (serum, urine)	82	N/N
11582	Chung 2015[95]	Sri Lanka, USA	Analytical	Laboratory (multisite, $n = 2$)	Adults	–	Cystatin C (urine)	42	N/N
967	Constantin 2010[36]	France	Clinical	Critical care (single)	Adults	RIFLE	NGAL (plasma)	88	Y/Y
981	Cruz 2010[96]	Italy	Clinical	Critical care (single)	Adults	RIFLE	NGAL (plasma)	301	Y/Y
599	Cullen 2012[97]	Ireland	Analytical	Laboratory (single)	Adults	–	NGAL (urine)	174	N/N
11388	Dai 2015[98]	China	Clinical	Critical care (single)	Adults	KDIGO	Cystatin C (plasma, urine)/NGAL (plasma, urine)	112	N/N
11338	De Berardinis 2015[99]	USA, Italy, France	Clinical/analytical	Emergency department (multisite, $n = 3$)	Adults	RIFLE	NGAL (plasma)	530	Y/Y
1645	de Geus 2011[37]	The Netherlands	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (plasma, urine)/NGAL (plasma, urine)	510	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
768	de Geus 2011[100]	The Netherlands	Clinical	Critical care (single)	Adults	RIFLE	NGAL (plasma, urine)	632	Y/Y
302	de Geus 2013[101]	The Netherlands	Clinical	Critical care (single)	Adults	AKIN	NGAL (plasma)	663	Y/Y
179	de Geus 2013[102]	The Netherlands	Clinical/analytical	Critical care (single)	Adults	AKIN	NGAL (urine)	481	N/N
139	Delanaye 2014[103]	France, Belgium	Clinical	Critical care (multisite, $n = 3$)	Adults	KDIGO	Cystatin C (serum)	51	N/N
1611	Delcroix 2013[104]	Belgium	Clinical	Cardiac (single)	Adults	KDIGO	NGAL (plasma, urine)	50	Y/Y
1624	Demirtas 2013[105]	Turkey	Clinical	Cardiac (single)	Adults	Not reported	NGAL (not specified)	72	N/N
1219	Dent 2007[106]	USA	Clinical/analytical	Cardiac (single)	Children	RIFLE	NGAL (plasma)	120	Y/Y
1600	Di Somma 2013[107]	Italy	Clinical	Emergency department (multisite, $n = 3$)	Adults	AKIN/RIFLE	NGAL (plasma)	665	Y/Y
669	Doi 2011[108]	Japan	Clinical	Critical care (single)	Adults	RIFLE	NGAL (urine)	339	N/N
1594	Doi 2013[109]	Japan	Clinical	Cardiac (multisite, $n = 2$)	Adults	AKIN	NGAL (plasma)	146	Y/Y
141	Doi 2014[110]	Japan	Clinical	Critical care (single)	Adults	RIFLE	NGAL (urine)	339	N/N
525	Ejaz 2012[111]	USA	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	100	N/N
408	El-Farghali 2012[112]	Egypt	Clinical	Critical care (single)	Children	AKIN	NGAL (serum)	60	Y/Y
1511	Fan 2014[113]	China	Clinical	Critical care (single)	Adults	RIFLE	NGAL (urine)	126	Y/Y
11667	Fanning 2015[114]	New Zealand	Clinical	Cardiac (single)	Adults	KDIGO	NGAL (serum, urine)	50	N/N
997	Felicio 2009[115]	Brazil	Clinical	Cardiac (single)	Adults	Not reported	Cystatin C (serum)	50	N/N
393	Fouad 2013[116]	Egypt	Clinical	Critical care (single)	Adults	AKIN/RIFLE	Cystatin C (serum)	100	N/N
1432	Gaipov 2015[117]	Turkey	Clinical	Cardiac (single)	Adults	KDIGO	NGAL (serum, urine)	60	Y/Y
75	Ghonemy 2014[38]	Egypt	Clinical	Cardiac (single)	Adults	RIFLE	Cystatin C (serum)/ NGAL (serum)	50	Y/Y
242	Glassford 2013[118]	Australia	Clinical/analytical	Critical care (single)	Adults	RIFLE	NGAL (plasma, urine)	102	N/N
11804	Gocze 2015[119]	Germany	Clinical	Critical care (single)	Adults	OTHER	Nephrocheck (urine)	107	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
961	Grenier 2010[120]	USA, Canada, the Netherlands	Analytical	Laboratory (multisite, $n = 3$)	Adults	–	NGAL (urine)	Unclear	N/N
4025	Guo 2011[121]	China	Clinical	Critical care (multisite, no numbers reported)	Adults	RIFLE	NGAL (urine)	92	N/N
1049	Haase 2009[31]	Australia	Clinical	Cardiac (single)	Adults	AKIN	Cystatin C (plasma)/ NGAL (urine)	100	Y/Y
1072	Haase-Fielitz 2009[39]	Australia	Clinical/analytical	Cardiac (single)	Adults	RIFLE	Cystatin C (plasma)/ NGAL (urine)	100	Y/Y
1020	Haase-Fielitz 2009[40]	Australia	Clinical/analytical	Cardiac (single)	Adults	AKIN/RIFLE	NGAL (plasma)	100	Y/Y
1622	Hamed 2013[122]	Egypt	Clinical	Critical care (single)	Children	RIFLE	Cystatin C (serum)	62	Y/Y
1062	Han 2009[41]	USA	Clinical/analytical	Cardiac (single)	Adults	AKIN (modified)	NGAL (urine)	90	Y/Y
142	Hansen 2014[123]	Denmark	Analytical	Laboratory (multisite, $n = 2$)	Adults	–	NGAL (plasma, urine)	68	N/N
526	Hassinger 2012[124]	USA	Clinical	Cardiac (single)	Children	RIFLE	Cystatin C (serum)	100	N/N
1059	Heise 2009[125]	Germany	Clinical	Cardiac (single)	Adults	National Kidney Foundation guideline	Cystatin C (serum)	50	N/N
1403	Herget-Rosenthal 2004[42]	Germany	Clinical/analytical	Critical care (single)	Adults	RIFLE	Cystatin C (serum)	85	Y/Y
1236	Hirsch 2007[126]	USA	Clinical/analytical	Cardiac (single)	Children	Other	NGAL (plasma, urine)	91	Y/Y
1440	Hjortrup 2015[43]	Denmark	Clinical	Critical care (multisite, $n = 3$)	Adults	KDIGO	NGAL (plasma, urine)	222	Y/Y
225	Hoffman 2013[127]	USA	Clinical/analytical	Critical care (single)	Children	Other	NGAL (urine)	62	Y/Y
207	Hong 2013[128]	South Korea	Clinical/analytical	Emergency department/critical care (single)	Adults	RIFLE	NGAL (plasma)	45	Y/Y
1488	Hoste 2014[44]	USA, Canada, Europe[a]	Clinical	Critical care (multisite, $n = 35$)	Adults	KDIGO	Nephrocheck (urine)	153	Y/Y

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
1574	In 2014[129]	South Korea	Clinical	Critical care (single)	Adults	RIFLE	NGAL (plasma)	126	Y/Y
1587	Jayaraman 2014[130]	India	Clinical	Cardiac (single)	Adults	RIFLE	NGAL (urine)	100	N/N
1531	Johansson 2014[131]	Sweden	Clinical	Cardiac (single)	Adults	RIFLE	Cystatin C (serum)	64	N/N
247	Kambhampati 2013[132]	USA	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	100	N/N
1601	Kashani 2013[45]	USA, Europe[a]	Clinical	Critical care (multisite, $n = 35$)	Adults	KDIGO	Nephrocheck (urine)	728	N/N
1139	Kato 2008[46]	Japan	Clinical	Critical care (single)	Adults	Other	Cystatin C (serum)	87	Y/Y
1609	Khosravi 2013[133]	Iran	Clinical	Critical care (single)	Adults	RIFLE	NGAL (serum)	90	Y/Y
67	Kidher 2014[47]	UK	Clinical/analytical	Cardiac (single)	Adults	RIFLE	NGAL (plasma)	53	Y/Y
137	Kiessling 2014[134]	Germany	Clinical/analytical	Cardiac (single)	Adults	AKIN	Cystatin C (serum)	70	N/N
296	Kift 2013[135]	UK	Analytical	Laboratory (single)	Adults	AKIN	NGAL (urine)	78	N/N
2189	Kim 2012[136]	South Korea	Clinical	Cardiac: contrast (single)	Adults	Other	Cystatin C (serum)	89	Y/Y
232	Kim 2013[137]	South Korea	Clinical	Emergency department/critical care (single)	Adults/ children	AKIN	NGAL (plasma)	231	N/N
720	Koch 2011[138]	Germany	Clinical	Cardiac (single)	Children	RIFLE	NGAL (plasma)	218	N/N
1889	Koeijers 2012[139]	Curaçao	Clinical	Critical care (single)	Adults	AKIN	NGAL (urine)	88	Y/Y
473	Kokkoris 2012[48]	Greece	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (plasma)/ NGAL (plasma, urine)	100	Y/Y
1127	Koyner 2008[140]	USA	Clinical	Cardiac (single)	Adults	Other	Cystatin C (plasma, urine)/NGAL (plasma, urine)	72	Y/Y
827	Koyner 2010[141]	USA	Clinical	Cardiac (single)	Adults	AKIN	Cystatin C (urine)/ NGAL (urine)	123	N/N
2483	Koyner 2012[142]	USA	Clinical	Cardiac (multisite, $n = 6$)	Adults	AKIN	NGAL (plasma, urine)	380	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
341	Koyner 2013[143]	USA	Clinical	Cardiac (multisite, $n = 8$)	Adults/ children	AKIN/RIFLE	Cystatin C (urine)	1502	N/N
3999	Koyner 2014[144]	USA, Europe[a]	Clinical	Critical care (multisite, $n = 35$)	Adults	KDIGO	Nephrocheck (urine)	692	N/N
11469	Koyner 2015[145]	USA	Clinical	Critical care (unclear)	Adults	AKIN	Nephrocheck (urine)/ NGAL (plasma, urine)	77	N/N
871	Krawczeski 2010[146]	USA	Clinical	Cardiac (single)	Children	RIFLE	Cystatin C (serum)	374	Y/Y
657	Krawczeski 2011[147]	USA	Clinical	Cardiac (single)	Children	AKIN/RIFLE	NGAL (urine)	220	N/N
745	Krawczeski 2011[148]	USA	Clinical/analytical	Cardiac (single)	Children	AKIN/RIFLE	NGAL (plasma, urine)	373	Y/Y
1961	Lacquaniti 2013[149]	Italy	Clinical	Cardiac: contrast (single)	Adults	Other	NGAL (serum, urine)	120	Y/Y
4002	Lagos-Arevalo 2014[150]	Canada	Clinical/analytical	Critical care (single)	Children	KDIGO	Cystatin C (serum, urine)/NGAL (urine)	160	Y/Y
840	Lassus 2010[151]	Finland	Clinical	Emergency department (multisite, $n = 14$)	Adults	AKIN/RIFLE	Cystatin C (serum)	292	Y/Y
5108	Legrand 2014[152]	USA, Italy	Clinical	Emergency department (multisite, $n = 2$)	Adults	RIFLE	Cystatin C (urine)/ NGAL (plasma)	87	N/N
5087	Legrand 2015[49]	France	Clinical	Critical care (single)	Adults	KDIGO	Cystatin C (plasma)/ NGAL (plasma, urine)	111	Y/Y
1500	Lewandowska 2014[153]	Poland	Clinical/analytical	Critical care (single)	Adults	RIFLE	NGAL (urine)	63	Y/Y
1650	Li 2010[154]	China	Clinical	Emergency department (single)	Adults	RIFLE	Cystatin C (serum)	71	N/N
1607	Li 2013[155]	China	Clinical	Critical care (single)	Adults	AKIN	NGAL (urine)	55	Y/Y
1035	Liangos 2009[50]	USA	Clinical/analytical	Cardiac (multisite, $n = 2$)	Adults	AKIN (modified)	Cystatin C (urine)/ NGAL (urine)	103	Y/Y
263	Liebetrau 2013[156]	Germany	Clinical/analytical	Cardiac (single)	Adults	KDIGO	Cystatin C (plasma)/ NGAL (urine)	141	N/N
97	Liebetrau 2014[157]	Germany	Clinical/analytical	Cardiac: contrast (single)	Adults	KDIGO	Cystatin C (plasma)/ NGAL (urine)	128	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
283	Linko 2013[51]	Finland	Clinical	Critical care (multisite, $n = 25$)	Adults	RIFLE	NGAL (plasma)	369	Y/Y
392	Liu 2013[52]	China	Clinical/analytical	Cardiac (single)	Adults	AKIN	NGAL (urine)	109	Y/Y
591	Macdonald 2012[158]	Australia	Clinical/analytical	Emergency department (multisite, $n = 2$)	Adults	RIFLE	NGAL (plasma)	102	Y/Y
237	Magro 2013[159]	Brazil	Clinical	Critical care (single)	Adults	AKIN/RIFLE	Cystatin C (serum)	121	N/N
275	Makris 2013[160]	Greece	Analytical	Laboratory (single)	Adults	–	Cystatin C (urine)	130	N/N
1434	Malyszko 2015[161]	Poland	Clinical	Cardiac: contrast (single)	Adults	Other	Cystatin C (serum)/ NGAL (serum, urine)	89	N/N
793	Manzano-Fernandez 2011[162]	Spain	Clinical/analytical	Unclear (single)	Adults	Other	Cystatin C (plasma)	20	Y/Y
1528	Marcelino 2014[163]	Portugal	Clinical	Critical care (single)	Adults	AKIN	NGAL (urine)	61	Y/Y
607	Martensson 2012[164]	Sweden	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (serum)	327	N/N
4001	Martensson 2014[165]	Australia	Clinical	Critical care (single)	Adults	RIFLE	NGAL (urine)	102	N/N
1519	Matsa 2014[166]	UK	Clinical	Critical care (single)	Adults	RIFLE	NGAL (plasma, urine)	194	Y/Y
534	McCullough 2012[167]	USA	Clinical	Cardiac: contrast (multisite, $n = 3$)	Adults	Other	NGAL (plasma)	63	N/N
979	McIlroy 2010[53]	USA	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	426	Y/Y
11593	McIlroy 2015[168]	USA	Clinical	Cardiac (single)	Adults	KDIGO	NGAL (urine)	603	Y/Y
1568	Meersch 2014[54]	Germany	Clinical	Cardiac (single)	Adults	KDIGO	Nephrocheck (urine)/ NGAL (urine)	50	Y/Y
1485	Meersch 2014[55]	Germany	Clinical	Cardiac (single)	Children	RIFLE	Nephrocheck (urine)/ NGAL (urine)	51	Y/Y
1592	Merrikhi 2014[169]	Iran	Clinical	Critical care (single)	Children	RIFLE	NGAL (plasma, urine)	50	Y/Y
1369	Mishra 2005[170]	USA	Clinical	Cardiac (single)	Children	Other	NGAL (serum, urine)	71	Y/Y
5578	Mortara 2013[171]	Italy	Clinical/analytical	Emergency department (single)	Adults	Other	NGAL (serum)	30	Y/Y

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
381	Munir 2013[56]	Pakistan	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	88	Y/Y
1628	Murty 2013[172]	India	Clinical	Unclear (single)	Adults	RIFLE	Cystatin C (serum)	330	N/N
1058	Naruse 2009[173]	Japan	Clinical/analytical	Unclear (single)	Adults	K/DOQI	Cystatin C (serum)	328	N/N
864	Nejat 2010[57]	New Zealand	Clinical/analytical	Critical care (multisite, $n = 2$)	Adults	AKIN	Cystatin C (plasma)	444	N/N
885	Nejat 2010[174]	New Zealand	Clinical/analytical	Critical care (multisite, $n = 2$)	Adults	AKIN	Cystatin C (plasma, urine)	444	Y/Y
544	Nejat 2012[175]	Australia	Clinical	Critical care (multisite, $n = 2$)	Adults	AKIN	Cystatin C (urine)/ NGAL (urine)	489	N/N
6561	Nemes 2010[176]	Hungary	Clinical	Critical care (single)	Adults	Other	Cystatin C (serum)	105	Y/Y
1166	Nickolas 2008[177]	USA	Clinical/analytical	Emergency department (single)	Adults	RIFLE	NGAL (urine)	635	Y/Y
624	Nickolas 2012[178]	USA, Germany	Clinical/analytical	Emergency department (multisite, $n = 3$)	Adults	RIFLE	Cystatin C (urine)/ NGAL (urine)	1635	Y/Y
64	Nisula 2014[179]	Finland	Clinical	Critical care (multisite, no numbers reported)	Adults	KDIGO	NGAL (urine)	1042	Y/Y
554	Oh 2012[58]	South Korea	Clinical	Cardiac (single)	Adults	Other	NGAL (urine)	71	Y/Y
72	Omerika 2014[180]	Bosnia Herzegovina	Clinical	Cardiac (single)	Adults	RIFLE	NGAL (urine)	150	N/N
4004	Ortuno-Anderiz 2015[181]	Spain	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (plasma)	50	N/N
1578	Ozkan 2014[182]	Turkey	Clinical	Emergency department (single)	Adults	Not reported	NGAL (serum)	100	N/N
11344	Palazzuoli 2015[59]	Italy	Clinical	Unclear (single)	Adults	AKIN	Cystatin C (plasma)/ NGAL (plasma)	203	Y/Y
695	Parikh 2011[60]	USA, Canada	Clinical	Cardiac (multisite, $n = 6$)	Adults	RIFLE	NGAL (plasma, urine)	1219	Y/Y
348	Park 2013[183]	South Korea	Clinical	Unclear (single)	Adults	AKIN	Cystatin C (plasma, urine)	213	Y/Y

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
1453	Park 2015[61]	South Korea	Clinical	Cardiac (single)	Adults	RIFLE	NGAL (plasma)	189	Y/Y
252	Peco-Antic 2013[184]	Serbia	Clinical	Cardiac (single)	Children	RIFLE	Cystatin C (serum)/ NGAL (serum, urine)	112	N/N
875	Pedersen 2010[185]	Denmark	Analytical	Cardiac (single)	Adults/ children	–	NGAL (plasma, urine)	17	N/N
1004	Perianayagam 2009[186]	USA	Clinical/analytical	Critical care (multisite, $n = 2$)	Adults	Other	Cystatin C (serum)	200	N/N
3997	Perrotti 2015[62]	France	Clinical	Cardiac (single)	Adults	Other	NGAL (plasma)	166	Y/Y
921	Perry 2010[63]	USA	Clinical	Cardiac (multisite, $n = 2$)	Adults	ADQI Group consensus	NGAL (plasma)	879	Y/Y
11359	Petrovic 2015[187]	Serbia	CEA	Cardiac (single)	Children	RIFLE	Cystatin C (serum)/ NGAL (urine)	112	Y/Y
260	Pickering 2013[188]	New Zealand	Clinical	Critical care (multisite, $n = 2$)	Adults	KDIGO	Cystatin C (plasma, urine)/NGAL (plasma, urine)	528	N/N
13	Pipili 2014[189]	Greece	Clinical	Critical care (single)	Adults	RIFLE	Cystatin C (serum)/ NGAL (urine)	106	N/N
11327	Prowle 2015[64]	Australia	Clinical	Cardiac (single)	Adults	RIFLE	Cystatin C (serum)/ NGAL (urine)	93	Y/Y
11325	Ralib 2014[190]	New Zealand	Clinical	Emergency department (single)	Adults	KDIGO	Cystatin C (plasma, urine)/NGAL (plasma, urine)	77	N/N
11863	Rewa 2015[191]	Canada	Clinical	Critical care (multisite, $n = 5$)	Adults	KDIGO (modified)	NGAL (whole blood)	227	Y/Y
615	Ribichini 2012[192]	Italy	Clinical/analytical	Cardiac: contrast (single)	Adults	Other	Cystatin C (serum)	166	Y/Y
442	Ricci 2012[193]	Italy	Clinical	Cardiac (single)	Children	RIFLE	NGAL (whole blood)	160	Y/Y
978	Ristikankare 2010[194]	Finland	Clinical	Cardiac (single)	Adults	RIFLE	Cystatin C (serum)	110	N/N
790	Royakkers 2011[195]	The Netherlands	Clinical	Critical care (multisite, $n = 5$)	Adults	RIFLE	Cystatin C (serum, urine)	151	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
1638	Royakkers 2012[196]	The Netherlands	Clinical	Critical care (multisite, $n = 5$)	Adults	RIFLE	NGAL (serum, urine)	140	N/N
11514	Ruf 2015[197]	Germany	Clinical	Cardiac (single)	Children	RIFLE	Cystatin C (serum)/ NGAL (plasma, urine)	59	N/N
5666	Rybi-Szuminska 2013[198]	Poland	Analytical	Laboratory (multisite, no numbers reported)	Children	–	NGAL (urine)	172	N/N
10309	Sagheb 2014[199]	Iran	Clinical	Critical care (single)	Adults	Other	Cystatin C (serum)	80	N/N
465	Sargentini 2012[65]	Italy	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	52	Y/Y
11626	Schaub 2015[200]	USA, Canada	Clinical	Cardiac (multisite, $n = 6$)	Adults	AKIN	NGAL (urine)	959	N/N
316	Schinstock 2013[201]	USA	Clinical/analytical	Emergency department (single)	Adults	AKIN	NGAL (urine)	363	Y/Y
432	Schnell 2012[202]	France	Clinical	Critical care (multisite, $n = 2$)	Adults	AKIN	Cystatin C (serum, urine)	58	N/N
386	Seitz 2013[203]	Germany	Clinical	Cardiac (single)	Children	RIFLE	Cystatin C (serum)/ NGAL (urine)	139	Y/Y
899	Shapiro 2010[204]	USA	Clinical	Emergency department (multisite, $n = 10$)	Adults	RIFLE	NGAL (plasma)	661	Y/Y
654	Shaw 2011[205]	USA	CEA	Cardiac (unclear)	Adults	RIFLE	NGAL (urine)	Unclear	Y/Y
1649	Shi 2010[206]	China	Clinical	Critical care (multisite, $n = 2$)	Adults	AKIN	Cystatin C (serum)	98	N/N
705	Shlipak 2011[207]	USA	Clinical	Cardiac (multisite, $n = 6$)	Adults	AKIN	Cystatin C (serum)	1147	N/N
463	Shrestha 2012[207]	USA	Clinical	Critical care (single)	Adults	AKIN/RIFLE (simplified)	NGAL (serum, urine)	93	Y/Y
3995	Shum 2015[66]	China	Clinical	Critical care (single)	Adults	AKIN	NGAL (plasma)	151	Y/Y
1040	Siew 2009[209]	USA	Clinical	Critical care (single)	Adults	AKIN	NGAL (urine)	391	N/N
230	Siew 2013[210]	USA	Clinical/analytical	Critical care (single)	Adults	AKIN	Cystatin C (urine)/ NGAL (urine)	352	N/N

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
598	Sohrabian 2012[211]	Sweden	Analytical	Laboratory (single)	Adults	–	Cystatin C (urine)	41	N/N
857	Soto 2010[212]	Portugal	Clinical	Emergency department (single)	Adults	AKIN/RIFLE	Cystatin C (plasma, urine)	616	Y/Y
187	Soto 2013[213]	Portugal	Clinical	Emergency department (single)	Adults	AKIN/RIFLE	Cystatin C (serum)/ NGAL (plasma)	616	Y/Y
11842	Soyler 2015[214]	Turkey	Clinical	Emergency department (single)	Adults	AKIN	NGAL (urine)	100	Y/Y
439	Spahillari 2012[215]	USA	Clinical	Cardiac (multisite, $n = 6$)	Adults	Other	Cystatin C (plasma)	1150	N/N
750	Svenmarker 2011[216]	Sweden	Clinical	Cardiac (unclear)	Adults	Other	Cystatin C (serum)	98	N/N
185	Tasanarong 2013[217]	Thailand	Clinical	Cardiac: contrast (single)	Adults	KDIGO	NGAL (urine)	130	Y/Y
613	Torregrosa 2012[218]	Spain	Clinical/analytical	Critical care (single)	Adults	RIFLE	Cystatin C (urine)/ NGAL (urine)	135	Y/Y
1080	Tuladhar 2009[67]	UK	Clinical	Cardiac (single)	Adults	ADQI Group consensus	NGAL (plasma, urine)	50	Y/Y
11329	Tung 2015[68]	Taiwan	Clinical	Cardiac (single)	Adults	AKIN	Cystatin C (serum)/ NGAL (serum)	189	Y/Y
11765	Tziakas 2015[69]	Greece	Clinical/analytical	Cardiac (multisite, $n = 3$)	Adults	AKIN/RIFLE/ KDIGO	Cystatin C (plasma, urine)/NGAL (plasma, urine)	805	Y/Y
11253	Varela 2015[70]	Argentina	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	66	Y/Y
1371	Villa 2005[71]	Spain	Clinical	Critical care (single)	Adults	Other	Cystatin C (serum)	50	N/N
11382	Volpon 2015[219]	Brazil	Clinical	Critical care (single)	Children	RIFLE	Cystatin C (serum)	122	Y/Y
136	Wacker-Gusmann 2014[220]	Germany	Clinical	Cardiac: contrast (unclear)	Adults	AKIN/RIFLE	Cystatin C (serum)	373	N/N
1307	Wagener 2006[221]	USA	Clinical	Cardiac (single)	Adults	ADQI Group consensus	NGAL (urine)	81	Y/Y
1138	Wagener 2008[72]	USA	Clinical	Cardiac (single)	Adults	AKIN	NGAL (urine)	426	Y/Y

Study				Population			Biomarker		
ID	First author	Location	Outcome area	Setting (sites)	Population	Classification	Analyte	Subjects (AKI)	Sensitivity/ specificity
224	Wai 2013[222]	USA	Clinical	Critical care (single)	Children	RIFLE	NGAL (urine)	60	Y/Y
882	Wald 2010[223]	USA, Canada	Clinical/analytical	Cardiac (multisite, $n = 3$)	Adults	AKIN (modified)	Cystatin C (plasma)	150	N/N
6718	Wang 2009[224]	China	Clinical/analytical	Cardiac (single)	Adults	Other	Cystatin C (serum)	61	Y/Y
1486	Wang 2014[225]	China	Clinical	Cardiac (single)	Adults	AKIN	Cystatin C (serum)	616	N/N
1548	Wang 2014[226]	China	Clinical/analytical	Critical care (single)	Adults	AKIN	Cystatin C (serum)	446	Y/Y
11832	Westhoff 2015[227]	Germany	Clinical	Critical care (single)	Children	RIFLE	Nephrocheck (urine)	133	Y/Y
1183	Wheeler 2008[228]	USA	Clinical	Critical care (multisite, no numbers reported)	Children	Other	NGAL (serum)	143	Y/Y
218	Xiang 2013[229]	China	Analytical	Laboratory (single)	Adults	–	NGAL (serum)	454	N/N
291	Yin 2013[230]	China	Clinical	Cardiac (single)	Adults	Other	Cystatin C (serum)	204	Y/Y
1619	Yoon 2013[231]	South Korea	Clinical	Cardiac: contrast (single)	Adults	Other	Cystatin C (not specified)	723	Y/Y
1613	Youssef 2013[232]	Egypt	Clinical	Critical care (single)	Children	RIFLE	NGAL (serum)	75	Y/Y
1222	Zappitelli 2007[233]	USA	Clinical	Critical care (single)	Children	RIFLE	NGAL (urine)	140	Y/Y
700	Zappitelli 2011[234]	USA, Canada	Clinical/analytical	Cardiac (multisite, $n = 3$)	Children	AKIN	Cystatin C (plasma)	288	N/N
11263	Zappitelli 2015[235]	USA, Canada	Clinical/analytical	Critical care (multisite, $n = 3$)	Children	KDIGO	Cystatin C (serum)/ NGAL (urine)	287	N/N
243	Zheng 2013[236]	China	Clinical/analytical	Cardiac (single)	Children	AKIN (modified)	Cystatin C (serum)	43	Y/Y
11825	Zwiers 2015[237]	The Netherlands	Clinical/analytical	Critical care (single)	Children	RIFLE	NGAL (urine)	100	Y/Y

–, not applicable; ADQI, Acute Dialysis Quality Initiative; K/DOQI, Kidney Disease Outcomes Quality Initiative (of the National Kidney Foundation); N, no; Y, yes.
a Austria, Belgium, France, Germany, Spain, Sweden and the UK.

Appendix 7 Full performance measures quality assessment forms for the Nephrocheck case studies

Bihorac *et al.*[33]

Reference ID: 82 Reviewer initials: MM/BK Data entered: 23 May 2016

Citation

Authors: Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, DeMuth GE, *et al.*

Title: Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication

Journal: *American Journal of Respiratory and Critical Care Medicine* Year: 2014 Pages: 932–9 Vol.: 189(8)

Description of the measurement procedure

Features	Index	Reference
Name of analyte	Nephrocheck	Creatinine
Test name	Nephrocheck	Jaffe method
Test platform/method used	Astute 140 Meter	Roche COBAS Modular D
Manufacturer	Astute Medical	Roche
Sample matrix used [e.g. urine, serum, plasma (including type)]	Urine	Serum
Pre-analytical biological		
Patient state (e.g. fed/fasted, sitting/standing, rested)	Not described	Not described
Patient preparation	The presence of an indwelling urinary catheter was also a prerequisite	Not described
Anatomical site and/or mechanism	Catheter and urometer	Direct venepuncture via other available venous access or via an indwelling arterial line
Timing of sampling (e.g. before 0900)	Within 60 minutes of serum sample	Not described
Pre-analytical technical		
Sample collection (mechanism and use of stabilisation)	Urine samples were collected in standard (non-coated) specimen cups	Blood was collected in clot activator blood collection tubes (for serum)
Preprocessing handling, temperature, transport and time	For subjects with indwelling bladder catheters, the collection bag was first emptied and then a fresh sample of urine was collected; alternatively, the sample could be taken from a urometer, if present	Not described
Sample processing (e.g. preservation, centrifugation conditions, timings and temperature)	Urine was centrifuged (10 minutes at 1000*g*) to remove any cells or other debris and was then aliquoted and frozen	Serum was prepared by centrifugation for 10 minutes at a minimum of 1300g after clotting and was then aliquoted and frozen
Storage (e.g. volume, temperature, duration, freeze–thaw cycles)	Frozen (on dry ice or liquid nitrogen) $\leq$ 2 hours from collection and stored at $\leq$ –70 °C	Frozen (on dry ice or liquid nitrogen) $\leq$ 2 hours from collection and stored at $\leq$ –70 °C
Postprocessing handling and transport	Samples were shipped on dry ice. Samples were thawed immediately prior to analysis	Samples were shipped on dry ice. Samples were thawed immediately prior to analysis

Description of the measurement procedure		
Features	**Index**	**Reference**
Consideration of differences between groups	All samples were collected through the same prospective collection. No obvious difference between AKI and non-AKI	All samples were collected through the same prospective collection. No obvious difference between AKI and non-AKI
Standard operating procedures or quality assurance	Samples were excluded if they were not collected within 60 minutes of the blood sample, they were not processed and frozen within 2 hours, < 15 ml of urine was collected, they were not properly labelled or they were not properly frozen	Samples were excluded if they were of insufficient volume, the wrong collection tube was used, they were haemolysed, they were incorrectly labelled, they were not collected within 60 minutes of the urine samples, they were not processed within 2 hours or they were not properly frozen
Other	Sponsor banked samples; shipped to laboratories for analysis	Sponsor banked samples; shipped to laboratories for analysis
Analytical factors		
Sample blinding procedure	Technicians masked to clinical data	Not described
Sample randomisation procedure	Not described	Not described
Batching	Not described	Not described
Reference control materials	Traceable to reference standard solutions that contain defined mass (concentration) of TIMP-2 and IGFBP-7 in accordance with EN ISO 17511	IDMS-traceable calibration
Quality assurance procedures	Two internal controls (one positive and one negative) were run automatically with every sample. If the automatic check of these internal controls showed that the control value results were not within predefined limits, the metre displayed an error message and the test result was not reported. These controls were in addition to external liquid controls (traceable to the same reference standard solutions as the test), which were run to verify test performance and operator proficiency	Not described
Patient inclusion/exclusion criteria	Critically ill adult patients within 24 hours of admission to an ICU. The presence of an indwelling urinary catheter was also a prerequisite for inclusion. Patients with documented AKI at the time of enrolment were excluded	Critically ill adult patients within 24 hours of admission to an ICU. The presence of an indwelling urinary catheter was also a prerequisite for inclusion. Patients with documented AKI at the time of enrolment were excluded
Test failure rate and reasons for test failure	2.9% (12/420): eight invalid or missing test results, four sample processing deviations	Not described
Technical replication	Urine from each subject was analysed at each of the three testing sites, producing triplicate test values for each sample	Serum samples were analysed for creatinine at a central laboratory

Performance evaluation		
Performance goals (for precision and bias including method of calculation)	Not described	Not described
Within-individual biological variation	Not described	Not described
Pre-analytical factors	Not described	Not described
Total measurement uncertainty	Not described	Not described
Analytical verification or full validation	Not described – manufacturer's data reported	Not described
Analytical sensitivity		
Method (brief description)	Manufacturer's data reported	Not described
Limit of blank (LOB)	Manufacturer's data reported	Not described
Limit of detection (LOD)	Manufacturer's data reported	Not described
Limit of quantitation (LOQ)	Manufacturer's data reported	Not described
Analytical selectivity		
Method (brief description)	Not described	Not described
Cross-reactivity	Not described	Not described
Interference	Not described	Not described
Carry-over	Not described	Not described
Trueness		
Method (brief description)	Not described	Not described
Bias	Not described	Not described
Precision		
Method (brief description including M-Factors: time, calibration, operator and equipment)	Manufacturer's data reported	Not described
Repeatability (range), CV%	Not described	Not described
Intermediate Imprecision (range), CV%	Not described	Not described
Reproducibility (range), CV%	Manufacturer's data reported	Not described
Linearity and working range	Manufacturer's data reported	Not described
Method (brief description)	Manufacturer's data reported	Not described
Other (e.g. lot to lot, antibody validation profile)	Not described	Not described

Signalling questions

Were measurement procedures different between groups?

- No, but it is not clear whether samples were measured randomly or in batches, which may have introduced a systematic bias

Were measurement procedures described in enough detail to be repeated?

- The urinary Nephrocheck test was generally reported in enough detail to be repeated
- However, several parameters required to repeat the serum creatinine reference test were not described

Were measurement factors appropriately controlled for?

- No; the manufacturer's kit insert identifies albumin and bilirubin as interferents and recommends 'caution in interpreting Nephrocheck results in patients with significant proteinuria or severe hyperbilirubinuria'. Albumin (proteinuria and haematuria) and bilirubin (to a lesser extent) are associated with AKI. No attempt was made to identify and exclude these samples
- Quality control procedures were not reported for the creatinine reference test
- No validation or verification of the measurement systems was reported
- No performance goals were reported

Signalling questions
Were measurement procedures applicable to the final clinical setting? • No, measurements were conducted at three sites and the median of three measurements was used to determine diagnostic accuracy. Only a single measurement at a single site would be used in clinical practice, which may lead to less precise measurements Samples were freeze–thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing
Risk of bias (yes, no, uncertain)
Unclear
Risk of irreproducibility (yes, no, uncertain)
High
Risk of inapplicability (yes, no, uncertain)
High

CV%, coefficient of variation; IDMS, isotope dilution mass spectrometry.

Meersch *et al.*

Reference ID:	1485	Reviewer initials:	BK/MM	Data entered:	13 May 2016
Citation					
Authors:	Meersch M, Schmidt C, Van Aken H, Rossaint J, Görlich D, Stege D, *et al.*				
Title:	Validation of cell-cycle arrest biomarkers for acute kidney injury after pediatric cardiac surgery				
Journal	*PLOS ONE*	Year:	2014	Pages:	e110865
		Vol:	9 (10)		

Description of the measurement procedure		
Name of analyte	Nephrocheck	Creatinine
Test name	Nephrocheck	
Test platform/method used	Astute 140 Meter	
Manufacturer	Astute Medical	
Sample matrix used [e.g. urine, serum, plasma (including type)]	Urine	Serum
Pre-analytical biological		
Patient state (e.g. fed/fasted, sitting/standing, rested)	Not described	Not described
Patient preparation	Not described	Not described
Anatomical site and/or mechanism	Not described	Not described
Time of sampling (e.g. before 0900)	Immediately before and at 4 and 24 hours post CPB	Routinely measured before surgery, immediately after surgery and at least daily in the postoperative period
Pre-analytical technical		
Sample collection (mechanism and use of stabilisation)	Not described	Not described
Preprocessing handling, temperature, transport and time	Not described	Not described

Description of the measurement procedure		
Sample processing (e.g. preservation, centrifugation conditions, timings and temperature)	Not described	Not described
Storage (e.g. volume, temperature, duration, freeze–thaw cycles)	Stored in aliquots at –80 °C. Length of storage not described	Not described
Postprocessing handling and transport	Not described	Not described
Consideration of differences between groups	Nephrocheck and creatinine tests not performed at the same time	Nephrocheck and creatinine tests not performed at the same time
Standard operating procedures or quality assurance	Not described	Not described
Other		
Analytical factors		
Sample blinding	Laboratory investigators blinded to clinical outcomes	Laboratory investigators blinded to clinical outcomes
Sample randomisation	Not described	Not described
Batching	Not described	Not described
Reference control materials	Not described	Not described
Quality assurance procedures	Not described	Not described
Patient inclusion/exclusion criteria	All patients aged < 18 years undergoing cardiac surgery with CPB at the authors' centre between July 2013 and December 2013 were approached for study inclusion. Patients with severe pre-existing renal insufficiency (serum creatinine two times the age-adjusted normal range) were excluded	All patients aged < 18 years undergoing cardiac surgery with CPB at the authors' centre between July 2013 and December 2013 were approached for study inclusion. Patients with severe pre-existing renal insufficiency (serum creatinine two times the age-adjusted normal range) were excluded
Test failure rate and reasons for test failure	Not described	Not described
Performance evaluation		
Performance goals (for precision and bias including method of calculation)	Not described	Not described
Within-individual biological variation	Not described	Not described
Pre-analytical factors	Not described	Not described
Total measurement uncertainty	Not described	Not described
Analytical verification or full validation	Not described	Not described
Analytical sensitivity		
Method (brief description)	Not described	Not described
Limit of blank (LOB)	Not described	Not described
Limit of detection (LOD)	Not described	Not described
Limit of quantitation (LOQ)	Not described	Not described
Analytical specificity		
Method (brief description)	Not described	Not described
Cross-reactivity	Not described	Not described
Interference	Not described	Not described
Carry-over	Not described	Not described

Performance evaluation		
Trueness		
Method (brief description)	Not described	Not described
Bias	Not described	Not described
Precision		
Method (brief description including M-factors: time, calibration, operator and equipment)	Not described	Not described
Repeatability (range), CV%	Not described	Not described
Intermediate imprecision (range), CV%	Not described	Not described
Reproducibility (range), CV%	Not described	Not described
Linearity and working range	Not described	Not described
Method (brief description)	Not described	Not described
Other (e.g. lot to lot, antibody validation profile)	Not described	Not described

Signalling questions

Were measurement procedures different between groups?

- Uncertain. Pre-analytical and analytical study procedures were not reported in enough detail to be confident that systematic bias between the groups had been avoided, for example no details were reported concerning sample randomisation and batching. However, laboratory investigators were blinded to clinical outcomes
- Index and reference test samples were collected at different times. It is unclear whether this may have introduced a bias

Were measurement procedures described in enough detail to be repeated?

- No; very limited data were provided concerning the Nephrocheck test and only the analyte name, matrix and time points were provided for creatinine

Were measurement factors appropriately controlled for?

- No. Albumin, bilirubin and methylene blue are known Nephrocheck interferents that were not controlled for in the urine samples
- Quality control procedures were not reported for either the index test or the reference test
- The method for and traceability of the reference test were not described
- The performance characteristics of the index test and reference test were not described
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was performed
- No performance goals were reported

Were measurement procedures applicable to the final clinical setting?

- No. The test was performed in patients aged < 18 years of age, which contradicts the instructions for use
- Samples were frozen and thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles, but the manufacturer suggests avoiding repeated freezing and thawing

Risk of bias (high, low, unclear)

Unclear

Risk of irreproducibility (high, low, unclear)

High

Risk of inapplicability (high, low, unclear)

High

CV%, coefficient of variation.

Hoste *et al.*[44]

Reference ID:	1488	Reviewer initials:	MM/BK	Data entered:	18 May 2016

Citation

Authors:	Hoste EAJ, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, *et al.*				
Title:	Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers				
Journal:	*Nephrology Dialysis Transplantation*	Year:	2014	Pages:	2054–61
		Vol:	29		

Description of the measurement procedure

Features	Index	Reference
Name of analyte	Nephrocheck	Creatinine
Test name	Nephrocheck	
Test platform/method used	Astute 140 Meter	Not described
Manufacturer	Astute Medical	Not described
Sample matrix used [e.g. urine, serum, plasma (including type)]	Urine	Serum
Pre-analytical biological		
Patient state (e.g. fed/fasted, sitting/standing, rested)	Not described	Not described
Patient preparation	Urinary catheter	Not described
Anatomical site and/or mechanism	Urinary catheter	Not described
Time of sampling (e.g. before 0900)	'At enrolment' (unclear if within 1 hour)	Not described
Pre-analytical technical		
Sample collection (mechanism and use of stabilisation)	'Standard methods'	Not described
Preprocessing handling, temperature, transport and time	Collected either directly from catheter or from collection bag (emptied first)	Not described
Sample processing (e.g. preservation, centrifugation conditions, timings and temperature)	Centrifugation (10 minutes at 1000*g*)	Not described
Storage (e.g. volume, temperature, duration, freeze–thaw cycles)	Frozen within 2 hours of collection, stored at ≤ 70 °C (length of storage not described)	Not described
Postprocessing handling and transport	Transport not described. Thawed immediately prior to analysis	Not described
Consideration of differences between groups	Prospective data used for Nephrocheck, sometimes retrospective data used for creatinine	In some patients the baseline creatinine value was used (two different methods for determining baseline) rather than the creatinine value at the time of enrolment
Standard operating procedures or quality assurance	Operators required to complete proficiency training using control samples. No other quality assurance described	Not described

Description of the measurement procedure		
Features	**Index**	**Reference**
Other		
Analytical factors		
Sample blinding	Technicians blinded to clinical data	Blinded to final determination of AKI status
Sample randomisation	Not described	Not described
Batching	Not described	Not described
Reference control materials	Traceable to reference standard solutions in accordance with ISO 17511	Not described
Quality assurance procedures	Two detection zones used as internal controls (one positive and one negative control) and run automatically with every sample, in addition to external liquid controls (traceable to the same reference standard solutions as the test), which are run to verify test performance and operator proficiency	Not described
Patient inclusion/exclusion criteria		
Test failure rate and reasons for test failure	$n = 7/744$ Sapphire patients with invalid or missing test results	Not described
Performance evaluation		
Performance goals (for precision and bias including method of calculation)	Not described	Not described
Within-individual biological variation	Not described	Not described
Pre-analytical factors	Not described	Not described
Total measurement uncertainty	Not described	Not described
Analytical verification or full validation	Not described – manufacturer's data reported	Not described
Analytical sensitivity		
Method (brief description)	Not described	Not described
Limit of blank (LOB)	Manufacturer's data reported	Not described
Limit of detection (LOD)	Manufacturer's data reported	Not described
Limit of quantitation (LOQ)	Manufacturer's data reported	Not described
Analytical specificity		
Method (brief description)	Not described	Not described
Cross-reactivity	Not described	Not described
Interference	Not described	Not described
Carry-over	Not described	Not described
Trueness		
Method (brief description)	Not described	Not described
Bias	Not described	Not described

Performance evaluation		
Precision		
Method (brief description including M-factors: time, calibration, operator and equipment)	Manufacturer's data reported	Not described
Repeatability (range), CV%	Not described	Not described
Intermediate Imprecision (range), CV%	Not described	Not described
Reproducibility (range), CV%	Manufacturer's data reported	Not described
Linearity and working range	Manufacturer's data reported	Not described
Method (brief description)	Manufacturer's data reported	Not described
Other (e.g. lot to lot, antibody validation profile)	Not described	Not described

Signalling questions

Were measurement procedures different between groups?

- Pre-analytical procedures were described in adequate detail and did not appear to differ between patient groups
- Although laboratory investigators were blinded to clinical outcomes, it is unclear whether samples were batched or randomised for analysis
- The index and reference test samples were collected at different times. It is unclear whether this may have introduced a bias

Were measurement procedures described in enough detail to be repeated?

- The urinary Nephrocheck test was reported in enough detail to be repeated, although it is not clear whether the measurements were performed in a single batch and randomised
- In addition, it is not clear how long the samples were frozen for
- Several parameters required to repeat the serum creatinine reference test were not described

Were measurement factors appropriately controlled for?

- No; albumin, bilirubin and methylene blue are known Nephrocheck interferents that were not controlled for in the urine samples. The manufacturer's kit insert recommends 'caution in interpreting Nephrocheck results in patients with significant proteinuria or severe hyperbilirubinuria'[304]
- Quality control procedures were not reported for the creatinine reference test. The method for and traceability of the reference test were not described
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was performed
- It is also not clear whether the samples were processed within 1 hour of collection
- The performance characteristics and goals of the reference test and index test were not described

Were measurement procedures applicable to the final clinical setting?

- Unclear. Samples were freeze–thawed prior to measurement in the study, whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were available on freeze–thaw cycles but the manufacturer suggests avoiding repeated freezing and thawing

Risk of bias (high, low, unclear)

Unclear

Risk of irreproducibility (high, low, unclear)

High

Risk of inapplicability (high, low, unclear)

Unclear

CV%, coefficient of variation.

Meersch *et al.*[54]

Reference ID:	1568	Reviewer initials:	MM/BK	Data entered:	19 May 2016

Citation

Authors:	Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, *et al.*				
Title:	Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery				
Journal:	*PLOS ONE*	Year:	2014	Pages:	e93460
		Vol:	9		

Description of the measurement procedure

Features	Index	Reference
Name of analyte	Nephrocheck	Creatinine
Test name	Nephrocheck	
Test platform/method used	Astute 140 Meter	
Manufacturer	Astute Medical	
Sample matrix used [e.g. urine, serum, plasma (including type)]	Urine	Serum
Pre-analytical biological		
Patient state (e.g. fed/fasted, sitting/standing, rested)	Not described	Not described
Patient preparation	Not described	Not described
Anatomical site and/or mechanism	Not described	Not described
Time of sampling (e.g. before 0900)	Pre CPB and 4, 12 and 24 hours after CPB	Pre CPB and 4, 12, 24, 48 and 72 hours post CPB and at time of discharge
Pre-analytical technical		
Sample collection (mechanism and use of stabilisation)	Not described	Not described
Preprocessing handling, temperature, transport and time	Not described	Not described
Sample processing (e.g. preservation, centrifugation conditions, timings and temperature)	Centrifuged immediately (further details not given)	Not described
Storage (e.g. volume, temperature, duration, freeze–thaw cycles)	Stored at ≤ -70 °C (duration not stated)	Not described
Postprocessing handling and transport	Thawed immediately prior to analysis	Not described
Consideration of differences between groups	Prospective data used for Nephrocheck, sometimes retrospective data used for creatinine	In some patients the baseline creatinine value was used rather than the creatinine value at the time of enrolment
Standard operating procedures or quality assurance	Not described	Not described
Other		
Analytical factors		
Sample blinding	Not described	Not described
Sample randomisation	Not described	Not described
Batching	Not described	Not described

Description of the measurement procedure		
Features	**Index**	**Reference**
Reference control materials	Not described	Not described
Quality assurance procedures	Not described	Not described
Patient inclusion/exclusion criteria	Those with a Cleveland Clinic Foundation Score of ≥ 6 were eligible for enrolment. Exclusion criteria included: 1. pregnancy 2. post-renal transplantation, 3. immunosuppressive therapy and 4. patients receiving corticosteroid therapy with a change in their dose within the past 2 weeks	Those with a Cleveland Clinic Foundation Score of ≥ 6 were eligible for enrolment. Exclusion criteria included: 1. pregnancy, 2. post-renal transplantation, 3. immunosuppressive therapy and 4. patients receiving corticosteroid therapy with a change in their dose within the past 2 weeks
Test failure rate and reasons for test failure	Not described	Not described
Performance evaluation		
Performance goals (for precision and bias including method of calculation)	Not described	Not described
Within-individual biological variation	Not described	Not described
Pre-analytical factors	Not described	Not described
Total measurement uncertainty	Not described	Not described
Analytical verification or full validation	Not described	Not described
Analytical sensitivity		
Method (brief description)	Not described	Not described
Limit of blank (LOB)	Not described	Not described
Limit of detection (LOD)	Not described	Not described
Limit of quantitation (LOQ)	Not described	Not described
Analytical specificity		
Method (brief description)	Not described	Not described
Cross-reactivity	Not described	Not described
Interference	Not described	Not described
Carry-over	Not described	Not described
Trueness		
Method (brief description)	Not described	Not described
Bias	Not described	Not described
Precision		
Method (brief description including M-factors: time, calibration, operator and equipment)	Not described	Not described
Repeatability (range), CV%	Not described	Not described
Intermediate Imprecision (range), CV%	Not described	Not described
Reproducibility (range), CV%	Not described	Not described
Linearity and working range	Not described	Not described
Method (brief description)	Not described	Not described
Other (e.g. lot to lot, antibody validation profile)	Not described	Not described

Signalling questions

Were measurement procedures different between groups?

- Uncertain. Pre-analytical and analytical study procedures were not reported in enough detail to be confident that bias had been avoided, for example no details were reported concerning sample blinding, randomisation and batching
- In some patients the baseline creatinine value was used rather than the creatinine value at the time of enrolment. It is not clear if this was systematically different between the patient groups

Were measurement procedures described in enough detail to be repeated?

- Limited details were provided concerning the Nephrocheck test; not enough details were provided to repeat the study
- Almost all parameters required to repeat the serum creatinine reference test were not described, not even the name and manufacturer of the assay

Were measurement factors appropriately controlled for?

- No. Albumin, bilirubin and methylene blue are known Nephrocheck interferents that were not controlled for in the urine samples
- Quality control procedures were not reported for Nephrocheck or for the creatinine reference test
- The method for and traceability of the reference test were not described
- The performance characteristics of the reference test and the index test were not described
- It is unclear whether the measurement systems were performing as specified by the manufacturer as no internal verification was reported
- No performance goals were reported

Were measurement procedures applicable to the final clinical setting?

- Unclear as the study procedures not described in enough detail
- Samples were frozen and thawed prior to measurement in the study whereas samples are likely to be analysed immediately (fresh) in the acute clinical context. No data were provided on freeze–thaw cycles but the manufacturer suggests avoiding repeated freezing and thawing

Risk of bias (high, low, unclear)

Unclear

Risk of irreproducibility (high, low, unclear)

High

Risk of inapplicability (high, low, unclear)

High

CV%, coefficient of variation.

Appendix 8 Search methods for the AKI-Diagnostics economic model literature review

Databases searched

- Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 2 of 12, February 2016)
- Database of Abstracts of Reviews of Effect (Wiley Online Library) (Issue 2 of 4, April 2015)
- EMBASE Classic + EMBASE (via Ovid) (1947 to 26 February 2015)
- Ovid MEDLINE (1946 to March Week 2 2016)
- Ovid MEDLINE In-Process & Other Non-Indexed Citations (23 March 2016)
- NHS Economic Evaluation Database (Wiley Online Library) (Issue 2 of 4, April 2015).

Example MEDLINE search

(Full search strategies used in all databases are available from the authors on request.)

Search strategy

1. Acute Disease/ and exp Kidney Diseases/ (8114)
2. acute kidney injury/ (35,209)
3. kidney tubular necrosis, acute/ (2292)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (8613)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (21,799)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3501)
7. aki.tw. (4196)
8. 'contrast induced nephropathy'.tw. (1099)
9. or/1-8 (55,186)
10. reperfusion injury/ (21,566)
11. reperfusion/ (4317)
12. exp Delayed Graft Function/ (832)
13. 'delayed graft function*'.tw. (2349)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (42,376)
15. or/10-14 (51,149)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (725,426)
17. 1 or 2 or 3 or 16 (733,668)
18. 15 and 17 (7807)
19. 9 or 18 [AKI] (60,934)
20. models, economic/ or models, econometric/ (11,379)
21. markov chain/ (10,943)
22. Decision Trees/ (9378)
23. decision support techniques/ (14,411)
24. microsimulat*.tw. (484)
25. (patient level adj8 simulat*).tw. (44)
26. (simulat* adj3 model*).tw. and decision*.mp. (1428)
27. (discrete event* adj5 simulat*).tw. (429)
28. (discrete event* adj8 model*).tw. (346)
29. (decision* adj5 model*).tw. (9343)
30. (model* adj5 markov*).tw. (8445)

31. ((econom* or cost or costs) adj6 model*).tw. (14,201)
32. 'state transition model*'.tw. (294)
33. ('transition probabilit*' and (state or states or model*)).tw. (1097)
34. or/20-33 [Econ models] (61,100)
35. 19 and 34 (118)

Appendix 9 Search methods for the AKI-Diagnostics economic model parameters literature review

Databases searched

Searches	Databases
AKI costs	• Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 7 of 12, July 2015) • Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 2 of 4, April 2015) • EMBASE Classic + EMBASE (via Ovid) (1947 to 15 July 2015) • Ovid MEDLINE (1946 to July Week 2 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (16 July 2015)
AKI utilities	• EMBASE Classic + EMBASE (via Ovid) (1947 to 27 July 2015) • Ovid MEDLINE (1946 to July Week 2 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (16 July 2015)
AKI risks	• Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 7 of 12, July 2015) • EMBASE Classic + EMBASE (via Ovid) (1947 to 30 July 2015) • Ovid MEDLINE (1946 to July Week 4 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (30 July 2015)
CKD costs	• Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 8 of 12, August 2015) • Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 2 of 4, April 2015) • EMBASE Classic + EMBASE (via Ovid) (1947 to 14 August 2015) • Ovid MEDLINE (1946 to August Week 1 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (14 August 2015) • NHS Economic Evaluation Database (via Wiley Online Library) (Issue 2 of 4, April 2015)
CKD utilities	• Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 8 of 12, August 2015) • Database of Abstracts of Reviews of Effect (via Wiley Online Library) (Issue 2 of 4, April 2015) • EMBASE Classic + EMBASE (via Ovid) (1947 to 17 August 2015) • Ovid MEDLINE (1946 to August Week 1 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (August 17, 2015) • NHS Economic Evaluation Database (via Wiley Online Library) (Issue 2 of 4, April 2015)
CKD risks	• Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 8 of 12, August 2015) • EMBASE Classic + EMBASE (via Ovid) (1947 to 2 September 2015) • Ovid MEDLINE (1946 to August Week 2 2015) • Ovid MEDLINE In-Process & Other Non-Indexed Citations (25 August 2015) • NHS Economic Evaluation Database (via Wiley Online Library) (Issue 2 of 4, April 2015)

Example MEDLINE searches

(Full search strategies used in all databases are available from the authors on request.)

Acute kidney injury costs

Search strategy

1. Acute Disease/ and exp Kidney Diseases/ (7907)
2. acute kidney injury/ (34,725)
3. kidney tubular necrosis, acute/ (2253)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (7745)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (22,094)

6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3518)
7. aki.tw. (3679)
8. 'contrast induced nephropathy'.tw. (1025)
9. or/1-8 (54,260)
10. reperfusion injury/ (21,127)
11. reperfusion/ (4276)
12. exp Delayed Graft Function/ (713)
13. 'delayed graft function*'.tw. (2205)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (41,542)
15. or/10-14 (50,057)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (715,951)
17. 1 or 2 or 3 or 16 (724,030)
18. 15 and 17 (7499)
19. 9 or 18 [AKI] (59,776)
20. exp Hospitalization/ (172,146)
21. Inpatients/ (14,321)
22. (ward or wards).tw. (39,848)
23. exp Hospitals/ (215,221)
24. hospital units/ or exp intensive care units/ (70,023)
25. hospital*.tw. (826,340)
26. 'high dependency'.tw. (785)
27. (critical adj2 care).tw. (17,692)
28. (intensive adj2 care).tw. (91,081)
29. (inpatient or inpatients).tw. (64,890)
30. or/20-29 [Hospital Wards] (1,093,337)
31. exp great britain/ (322,784)
32. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (843,719)
33. (british or english or scottish or welsh or irish).in,ti. (81,221)
34. (scotland or ireland).in,ti. (85,992)
35. (england not 'new england').in,ti. (53,958)
36. (wales not 'new south wales').in,ti. (32,677)
37. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (680,616)
38. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,486)
39. (manchester adj3 (USA or massach*)).in,ti. (328)
40. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6218)
41. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1167)
42. or/38-41 (28,187)
43. 37 not 42 (652,429)
44. (nhs or 'national health service').in,ti. (78,445)
45. or/31-36,43-44 (1,323,915)
46. 19 and 30 and 45 (503)
47. exp 'Costs and Cost Analysis'/ (191,630)
48. cost*.tw. (352,643)
49. budget*.tw. (18,103)
50. (price or prices or pricing).tw. (23,573)
51. (financial* adj4 burden*).tw. (2622)
52. (economic* adj4 burden*).tw. (5378)
53. expenditure*.tw. (36,926)
54. or/47-53 [Costs] (492,123)
55. 19 and 30 and 45 and 54 [AKI Wards UK Costs] (49)
56. limit 55 to yr='2010 -Current' (28)
57. 19 and 30 and 54 (479)

58. limit 57 to 'reviews (maximizes specificity)' (20)
59. 56 or 58 (48)

Acute kidney injury utilities

Search strategy

1. Acute Disease/ and exp Kidney Diseases/ (7907)
2. acute kidney injury/ (34,725)
3. kidney tubular necrosis, acute/ (2253)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (7745)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (22,094)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3518)
7. aki.tw. (3679)
8. 'contrast induced nephropathy'.tw. (1025)
9. or/1-8 (54,260)
10. reperfusion injury/ (21,127)
11. reperfusion/ (4276)
12. exp Delayed Graft Function/ (713)
13. 'delayed graft function*'.tw. (2205)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (41,542)
15. or/10-14 (50,057)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (715,951)
17. 1 or 2 or 3 or 16 (724,030)
18. 15 and 17 (7499)
19. 9 or 18 [AKI] (59,776)
20. exp great britain/ (322,784)
21. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (843,719)
22. (british or english or scottish or welsh or irish).in,ti. (81,221)
23. (scotland or ireland).in,ti. (85,992)
24. (england not 'new england').in,ti. (53,958)
25. (wales not 'new south wales').in,ti. (32,677)
26. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (680,616)
27. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,486)
28. (manchester adj3 (USA or massach*)).in,ti. (328)
29. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6218)
30. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1167)
31. or/27-30 (28,187)
32. 26 not 31 (652,429)
33. (nhs or 'national health service').in,ti. (78,445)
34. or/20-25,32-33 [UK] (1,323,915)
35. exp Health Status/ (113,246)
36. 'health status'.tw. (37,086)
37. 'Quality of Life'/ (128,885)
38. (hql or hqol or h qol or hrqol or hr qol).tw. (8334)
39. 'quality of life'.tw. (149,495)
40. 'questionnaire*'.tw. (301,418)
41. or/35-40 (558,180)
42. (utility or utilities).ti. (18,669)
43. (qaly or 'quality adjusted life year*').tw. (7053)
44. 42 or 43 (25,018)
45. 41 and 44 (8176)

46. ((utility or utilities) adj5 (hql or hqol or h qol or hrqol or hr qol or 'quality of life' or health* or score* or weight*)).ab. (4351)
47. (preference* adj5 (hql or hqol or h qol or hrqol or hr qol or 'quality of life' or health* or score* or weight*)).tw. (3981)
48. (sf6d or sf 6d or short form 6d or shortform 6d or sf sixd or sf six d).tw. (466)
49. (hui or hui1 or hui2 or hui3).tw. (904)
50. 'health utilities index*'.tw. (542)
51. *quality-adjusted life years/ (1625)
52. 'health related quality of life'.tw. (22,714)
53. quality-adjusted life years/ (7808)
54. QALY.tw. (4335)
55. (eq-5d* or eq5d* or euroqol*).tw. (4329)
56. or/45-55 [Utilities] (41,087)
57. 19 and 34 and 56 [AKI and UK and Utilities] (9)
58. 19 and 56 [AKI and Utilities] (54)
59. limit 58 to 'reviews (best balance of sensitivity and specificity)' (11)
60. limit 57 to yr='2010 -Current' (3)
61. 59 or 60 (14)

Acute kidney injury risks

Search strategy

1. Acute Disease/ and exp *Kidney Diseases/ (6067)
2. *acute kidney injury/ (26,477)
3. *kidney tubular necrosis, acute/ (1197)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (7787)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (22,104)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3519)
7. aki.tw. (3705)
8. 'contrast induced nephropathy'.tw. (1027)
9. or/1-8 (46,556)
10. *reperfusion injury/ (16,238)
11. *reperfusion/ (1132)
12. exp *Delayed Graft Function/ (373)
13. 'delayed graft function*'.tw. (2207)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (41,592)
15. or/10-14 (46,283)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (716,822)
17. 1 or 2 or 3 or 16 (720,726)
18. 15 and 17 (7033)
19. 9 or 18 [AKI] (51,801)
20. 'high dependency'.tw. (785)
21. (critical adj2 care).tw. (17,716)
22. (intensive adj2 care).tw. (91,210)
23. (inpatient or inpatients).tw. (65,020)
24. critical care/ (25,394)
25. critical illness/ (18,693)
26. Intensive Care/ (16,540)
27. exp intensive care units/ (61,237)
28. critical illness*.tw. (4877)
29. ICU.tw. (29,797)
30. 20 or 21 or 22 or 24 or 25 or 26 or 27 or 28 or 29 [ICU] (160,191)

31. likelihood functions/ (18,212)
32. markov chains/ (10,701)
33. odds ratio/ (66,036)
34. proportional hazards models/ (51,090)
35. risk/ (103,777)
36. logistic models/ (99,887)
37. risk assessment/ (189,789)
38. risk factors/ (612,509)
39. ((risk or risks or odds or proportion*) adj5 (mortality or death or stage*)).ti. (9334)
40. ((incidence or prevalen*) adj5 (mortality or death or stage*)).ti. (3039)
41. or/31-40 [Risks Odds Likelihood studies] (976,879)
42. meta-analysis/ (58,183)
43. sn.fs. (564,719)
44. 42 or 43 [Data set cohort or meta analysis studies] (617,723)
45. *hospitalization/ or *'length of stay'/ or *patient admission/ or *patient discharge/ or *patient readmission/ or *patient transfer/ (58,042)
46. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 (aki or 'acute kidney*')).ti. (394)
47. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 ('acute kidney*' or 'acute renal*' or 'acute nephr*' or 'acute tubular necrosis*')).ti. (603)
48. 46 or 47 [AKI Risks Title search] (634)
49. exp great britain/ (323,050)
50. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (845,318)
51. (british or english or scottish or welsh or irish).in,ti. (81,404)
52. (scotland or ireland).in,ti. (86,152)
53. (england not 'new england').in,ti. (54,012)
54. (wales not 'new south wales').in,ti. (32,731)
55. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (681,856)
56. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,549)
57. (manchester adj3 (USA or massach*)).in,ti. (330)
58. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6251)
59. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1172)
60. or/56-59 (28,287)
61. 55 not 60 (653,569)
62. (nhs or 'national health service').in,ti. (78,681)
63. or/49-54,61-62 [UK Filter] (1,326,014)
64. 9 and 30 and 41 and 44 and 63 [AKI ICU Risks Data sets UK] (12)
65. 19 and 30 and 45 and 63 [AKI ICU and Length of stay Discharged UK] (8)
66. 48 and 63 [AKI Risks UK Titles] (34)
67. 67 or/64–66 [Final AKI ICU Risks] (47)

Chronic kidney disease costs

Search strategy

1. Acute Disease/and exp Kidney Diseases/ (7918)
2. acute kidney injury/ (34,881)
3. kidney tubular necrosis, acute/ (2256)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (7865)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (22,132)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3525)
7. aki.tw. (3750)
8. 'contrast induced nephropathy'.tw. (1033)

9. or/1–8 (54,483)
10. reperfusion injury/ (21,228)
11. reperfusion/ (4287)
12. exp Delayed Graft Function/ (724)
13. 'delayed graft function*'.tw. (2217)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (41,727)
15. or/10–14 (50,280)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (718,566)
17. 1 or 2 or 3 or 16 (726,662)
18. 15 and 17 (7538)
19. 9 or 18 [AKI] (60,029)
20. exp Hospitalisation/ (173,062)
21. Inpatients/ (14,410)
22. (ward or wards).tw. (39,983)
23. exp Hospitals/ (215,922)
24. hospital units/or exp intensive care units/ (70,293)
25. hospital*.tw. (830,289)
26. 'high dependency'.tw. (789)
27. (critical adj2 care).tw. (17,765)
28. (intensive adj2 care).tw. (91,464)
29. (inpatient or inpatients).tw. (65,272)
30. or/20–29 [Hospital Wards] (1,098,124)
31. exp great britain/ (323,690)
32. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (850,035)
33. (british or english or scottish or welsh or irish).in,ti. (81,795)
34. (scotland or ireland).in,ti. (86,568)
35. (england not 'new england').in,ti. (54,183)
36. (wales not 'new south wales').in,ti. (32,822)
37. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (685,504)
38. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,635)
39. (manchester adj3 (USA or massach*)).in,ti. (339)
40. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6295)
41. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1182)
42. or/38–41 (28,436)
43. 37 not 42 (657,068)
44. (nhs or 'national health service').in,ti. (79,247)
45. or/31–36,43–44 (1,331,854)
46. 19 and 30 and 45 (513)
47. exp 'Costs and Cost Analysis'/ (192,502)
48. cost*.tw. (354,814)
49. budget*.tw. (18,180)
50. (price or prices or pricing).tw. (23,711)
51. (financial* adj4 burden*).tw. (2651)
52. (economic* adj4 burden*).tw. (5444)
53. expenditure*.tw. (37,118)
54. or/47–53 [Costs] (494,870)
55. 19 and 30 and 45 and 54 [AKI Wards UK Costs] (49)
56. limit 55 to yr = '2010 -Current' (28)
57. 19 and 30 and 54 (479)
58. limit 57 to 'reviews (maximises specificity)' (20)
59. 56 or 58 (48)
60. renal insufficiency, chronic/or exp kidney failure, chronic/ (90,923)

61. Chronic Disease/and exp Kidney Diseases/ (13,363)
62. (chronic kidney or chronic renal).tw. (50,765)
63. CKD.tw. (12,350)
64. (end stage renal or end stage kidney or endstage renal or endstage kidney).tw. (27,376)
65. (ESRF or ESKF or ESRD or ESKD).tw. (11,389)
66. exp Dialysis/ (22,640)
67. renal dialysis/or hemodiafiltration/or exp peritoneal dialysis/ (98,191)
68. renal replacement therapy/ (3833)
69. h?emodialysis.tw. (59,032)
70. peritonealdialysis.tw. (8)
71. dialysis.tw. (83,548)
72. (CAPD or CCPD).tw. (6461)
73. Kidney Transplantation/ (83,562)
74. ((renal or kidney*) adj3 transplant*).tw. (65,170)
75. or/60–74 [CKD or End stage or dialysis or transplants] (299,294)
76. exp *'Costs and Cost Analysis'/ (50,115)
77. cost*.ti. (81,585)
78. budget*.ti. (4877)
79. (price or prices or pricing).ti. (6778)
80. financ*.ti. (12,421)
81. economic*.ti. (30,984)
82. expenditure*.ti. (7616)
83. or/76–82 [Cost Specific] (159,833)
84. 45 and 83 and 75 (210)
85. limit 84 to yr = '2010 -Current' (69)
86. 83 and 75 (2194)
87. limit 86 to 'reviews (maximises specificity)' (52)
88. 85 or 87 [CKD Costs Reviews or Recent UK studies] (117)
89. 88 not 59 [CKD not AKI costs] (112)

Chronic kidney disease utilities

Search strategy

1. exp great britain/ (323,690)
2. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (850,035)
3. (british or english or scottish or welsh or irish).in,ti. (81,795)
4. (scotland or ireland).in,ti. (86,568)
5. (england not 'new england').in,ti. (54,183)
6. (wales not 'new south wales').in,ti. (32,822)
7. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (685,504)
8. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,635)
9. (manchester adj3 (USA or massach*)).in,ti. (339)
10. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6295)
11. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1182)
12. or/8–11 (28,436)
13. 7 not 12 (657,068)
14. (nhs or 'national health service').in,ti. (79,247)
15. or/1–6,13–14 (1,331,854)
16. renal insufficiency, chronic/or exp kidney failure, chronic/ (90,923)
17. Chronic Disease/and exp Kidney Diseases/ (13,363)
18. (chronic kidney or chronic renal).tw. (50,765)

19. CKD.tw. (12,350)
20. (end stage renal or end stage kidney or endstage renal or endstage kidney).tw. (27,376)
21. (ESRF or ESKF or ESRD or ESKD).tw. (11,389)
22. exp Dialysis/ (22,640)
23. renal dialysis/or hemodiafiltration/or exp peritoneal dialysis/ (98,191)
24. renal replacement therapy/ (3833)
25. h?emodialysis.tw. (59,032)
26. peritonealdialysis.tw. (8)
27. dialysis.tw. (83,548)
28. (CAPD or CCPD).tw. (6461)
29. Kidney Transplantation/ (83,562)
30. ((renal or kidney*) adj3 transplant*).tw. (65,170)
31. or/16–30 [CKD or End stage or dialysis or transplants] (299,294)
32. exp Health Status/ (113,928)
33. 'Quality of Life'/ (129,941)
34. 'health status'.tw. (37,306)
35. (hql or hqol or h qol or hrqol or hr qol).tw. (8435)
36. 'quality of life'.tw. (150,784)
37. 'questionnaire*'.tw. (303,559)
38. or/32–37 (562,053)
39. (utility or utilities).ti. (18,818)
40. 38 and 39 (2240)
41. ((utility or utilities) adj5 (hql or hqol or h qol or hrqol or hr qol or 'quality of life' or health* or score* or weight*)).ab. (4399)
42. (preference* adj5 (hql or hqol or h qol or hrqol or hr qol or 'quality of life' or health* or score* or weight*)).tw. (4018)
43. (sf6d or sf 6d or short form 6d or shortform 6d or sf sixd or sf six d).tw. (477)
44. (hui or hui1 or hui2 or hui3).tw. (913)
45. 'health utilities index*'.tw. (546)
46. quality-adjusted life-years/ (7915)
47. (qaly or 'quality-adjusted life-year*').tw. (7153)
48. 'health related quality of life'.tw. (22,942)
49. (eq-5d* or eq5d* or euroqol*).tw. (4398)
50. or/40–49 [Health Utilities] (41,544)
51. 15 and 31 and 50 (98)
52. limit 51 to yr = '2010 -Current' (51)
53. 31 and 50 (1140)
54. limit 53 to 'reviews (maximises specificity)' (52)
55. 52 or 54 [CKD Health Utilities Search] (98)
56. Acute Disease/and exp Kidney Diseases/ (7918)
57. acute kidney injury/ (34,881)
58. kidney tubular necrosis, acute/ (2256)
59. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (7865)
60. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (22,132)
61. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3525)
62. aki.tw. (3750)
63. 'contrast induced nephropathy'.tw. (1033)
64. or/56–63 (54,483)
65. reperfusion injury/ (21,228)
66. reperfusion/(4287)
67. exp Delayed Graft Function/ (724)
68. 'delayed graft function*'.tw. (2217)
69. (reperfusion adj5 (injur* or isch?emi*)).tw. (41,727)

70. or/65–69 (50,280)
71. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (718,566)
72. 56 or 57 or 58 or 71 (726,662)
73. 70 and 72 (7538)
74. 64 or 73 [AKI] (60,029)
75. 15 and 50 and 74 (9)
76. 50 and 74 (54)
77. limit 76 to 'reviews (best balance of sensitivity and specificity)' (11)
78. 75 or 77 (19)
79. 55 not 78 (96)

Chronic kidney disease risks

Search strategy

1. likelihood functions/ (18,331)
2. markov chains/ (10,769)
3. odds ratio/ (66,504)
4. proportional hazards models/ (51,509)
5. risk/ (104,119)
6. logistic models/ (100,507)
7. risk assessment/ (190,924)
8. risk factors/ (615,846)
9. ((risk or risks or odds or proportion*) adj5 (mortality or death or stage*)).ti. (9407)
10. ((incidence or prevalen*) adj5 (mortality or death or stage*)).ti. (3063)
11. or/1–10 [Risks Odds Likelihood studies] (982,161)
12. meta-analysis/ (58,864)
13. sn.fs. (568,088)
14. 12 or 13 [Data set cohort or meta analysis studies] (621,726)
15. exp great britain/ (324,006)
16. ('united king*' or uk or 'U.K.' or 'UK.' or 'U.K' or britain).in,ti. (850,727)
17. (british or english or scottish or welsh or irish).in,ti. (81,862)
18. (scotland or ireland).in,ti. (86,638)
19. (england not 'new england').in,ti. (54,221)
20. (wales not 'new south wales').in,ti. (32,839)
21. (london or manchester or birmingham or leeds or sheffield or liverpool or newcastle or edinburgh or glasgow or cardiff or oxford or bristol).in,ti. (686,055)
22. ((london adj2 ontario) or (london adj on) or new london).in,ti. (20,654)
23. (manchester adj3 (USA or massach*)).in,ti. (339)
24. (newcastle adj4 (australia* or 'new south wales' or nsw)).in,ti. (6308)
25. (liverpool adj4 (australia* or 'new south wales' or nsw)).in,ti. (1187)
26. or/22–25 (28,473)
27. 21 not 26 (657,582)
28. (nhs or 'national health service').in,ti. (79,391)
29. or/15–20,27–28 [UK Filter] (1,332,939)
30. renal insufficiency, chronic/or exp kidney failure, chronic/ (90,965)
31. Chronic Disease/and exp Kidney Diseases/ (13,364)
32. (chronic kidney or chronic renal).tw. (50,799)
33. CKD.tw. (12,359)
34. (end stage renal or end stage kidney or endstage renal or endstage kidney).tw. (27,394)
35. (ESRF or ESKF or ESRD or ESKD).tw. (11,393)
36. exp Dialysis/ (22,644)
37. renal dialysis/or hemodiafiltration/or exp peritoneal dialysis/ (98,226)

38. renal replacement therapy/ (3840)
39. h?emodialysis.tw. (59,057)
40. peritonealdialysis.tw. (8)
41. dialysis.tw. (83,581)
42. (CAPD or CCPD).tw. (6461)
43. Kidney Transplantation/ (83,595)
44. ((renal or kidney*) adj3 transplant*).tw. (65,203)
45. or/30–44 [CKD] (299,421)
46. 45 and 11 and 14 and 29 [CKD and risks and data set and UK] (259)
47. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 (ckd or 'chronic kidney' or 'chronic renal')).ti. (1377)
48. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 (end stage renal or end stage kidney or ESRF or ESKF or ESRD or ESKD)).ti. (599)
49. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 (h?emodialysis or peritonealdialysis or dialysis or CAPD or CCPD)).ti. (1714)
50. ((risk or risks or odds or proportion* or incidence or prevalen*) adj8 (renal or kidney*) adj3 transplant*).ti. (1572)
51. or/47–50 [CKD Risks Title search] (5157)
52. 46 and 51 (29)

Appendix 10 Search methods for early treatment/preventative strategies for acute kidney injury in the intensive care unit

Databases searched

- Cochrane Database of Systematic Reviews (via Wiley Online Library) (Issue 3 of 12, March 2016)
- Cochrane Central Register of Controlled Trials (via Wiley Online Library) (Issue 2 of 12, February 2016)
- EMBASE Classic+EMBASE (via Ovid) (1947 to 14 March 2016)
- Ovid MEDLINE (1946 to March Week 1 2016)
- Ovid MEDLINE In-Process & Other Non-Indexed Citations (14 March 2016).

Example MEDLINE search

(Full search strategies used in all databases are available from the authors on request.)

Search strategy

1. Acute Disease/and exp *Kidney Diseases/ (6286)
2. *acute kidney injury/ (26,908)
3. *kidney tubular necrosis, acute/ (1263)
4. (Acute adj3 (kidney disease* or kidney injury or kidney failure or kidney dysfunction)).tw. (8577)
5. (Acute adj3 (renal disease* or renal injury or renal failure or renal dysfunction)).tw. (21,792)
6. ((Acute adj3 (Tubular Necrosis or nephrotoxic*)) or 'nephrotoxic injur*').tw. (3501)
7. aki.tw. (4174)
8. 'contrast induced nephropathy'.tw. (1095)
9. or/1–8 (47,456)
10. *reperfusion injury/ (16,539)
11. *reperfusion/(1162)
12. exp *Delayed Graft Function/ (429)
13. 'delayed graft function*'.tw. (2348)
14. (reperfusion adj5 (injur* or isch?emi*)).tw. (42,315)
15. or/10–14 (47,193)
16. (renal or kidney* or nephr* or 'tubular necrosis' or aki).tw. (724,886)
17. 1 or 2 or 3 or 16 (729,011)
18. 15 and 17 (7293)
19. 9 or 18 [AKI] (52,903)
20. (HDU or 'high dependency').tw. (874)
21. (critical adj2 care).tw. (18,319)
22. (intensive adj2 care).tw. (93,030)
23. (inpatient or inpatients).tw. (66,467)
24. critical care/ (42,427)
25. critical illness/ (19,515)
26. Intensive Care/ (42,427)
27. exp intensive care units/ (62,277)
28. critical* ill*.tw. (31,178)
29. ICU.tw. (31,036)
30. or/20–29 [ICU] (235,133)

31. early diagnosis/ (18,720)
32. (early adj3 (treatment* or intervention* or involv*)).tw. (71,209)
33. (early adj3 onset).tw. (28,860)
34. (early adj3 (therapy or therapies)).tw. (12,709)
35. (early adj4 management).tw. (10,464)
36. early initiation.tw. (2380)
37. pre-emptive.tw. (1823)
38. or/31–37 [Early treatment] (138,435)
39. 19 and 30 and 38 (232)
40. (prevent* adj3 ('acute kidney injury' or 'acute kidney failure' or 'acute kidney disease' or AKI)).tw. (406)
41. acute kidney injury/pc (2634)
42. 40 or 41 [AKI prevention] (2824)
43. 30 and 42 (299)
44. 39 or 43 (505)
45. exp treatment outcome/ (738,812)
46. exp clinical trial/ (726,655)
47. effect*.ti. (1,483,694)
48. or/45–47 [Treatment effect] (2,629,847)
49. 44 and 48 [AKI ICU Early intervention or Prevention Treatment Effect] (125)
50. limit 44 to 'reviews (best balance of sensitivity and specificity)' (213)
51. 49 or 50 (310)
52. exp animals/not exp humans/ (4,201,019)
53. preconditioning.ti. (5874)
54. perioperative*.ti. (13,889)
55. or/52–54 [studies to remove] (4,216,305)
56. 51 not 55 (296)

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